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(71) Demandeur/Applicant:  
PITMY INTERNATIONAL N.V., AN  
(72) Inventeur/Inventor:  
MEYER, PETRUS JOHANNES, ZA  
(74) Agent: R. WILLIAM WRAY & ASSOCIATES

(54) Titre : AMELIORATION DE L'ACTION D'AGENTS ANTI-INFECTIEUX  
(54) Title: ENHANCEMENT OF THE ACTION OF ANTI-INFECTIVE AGENTS

(57) Abrégé/Abstract:

The invention provides a method of enhancing the action of a pharmaceutical agent selected from the group consisting of the group comprising antimicrobial agents, the anthelmintic agents and the anti-ectoparasitic agents, but excluding coal tar solution and H1-antagonist antihistamines, characterised in that the agent is formulated with an administration medium which comprises a solution of nitrous oxide gas in a pharmaceutically acceptable carrier solvent for the gas and which administration medium includes at least one fatty acid or ester or other suitable derivative thereof selected from the group consisting of oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, arachidonic acid, eicosapentaenoic acid [C20: 5ω3], decosahexaenoic acid [C22: 6ω3], ricinoleic acid and derivatives thereof selected from the group consisting of the C1 to C6 alkyl esters thereof, the glycerol-polyethylene glycol esters thereof and the reaction product of hydrogenated natural oils composed largely of ricinoleic acid based oils, such as castor oil with ethylene oxide.

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INTERNATIONAL N.V. [NL/NL]; Kaya Gob, Nicolaas  
Debrot 33, Bonaire (AN).

(72) Inventor; and

(75) Inventor/Applicant (for US only): MEYER, Petrus, Jo-  
hannes [ZA/ZA]; 24 Quail Street, 6573 Sedgefield (ZA).(74) Agent: LE ROUX, Marius; D M Kisch Inc, P.O. Box  
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(54) Title: ENHANCEMENT OF THE ACTION OF ANTI-INFECTIVE AGENTS

(57) Abstract: The invention provides a method of enhancing the action of a pharmaceutical agent selected from the group consist-  
ing of the group comprising antimicrobial agents, the anthelmintic agents and the anti-ectoparasitic agents, but excluding coal tar  
solution and H1-antagonist antihistamines, characterised in that the agent is formulated with an administration medium which com-  
prises a solution of nitrous oxide gas in a pharmaceutically acceptable carrier solvent for the gas and which administration medium  
includes at least one fatty acid or ester or other suitable derivative thereof selected from the group consisting of oleic acid, linoleic  
acid, alpha-linolenic acid, gamma-linolenic acid, arachidonic acid, eicosapentaenoic acid [C20: 5 $\omega$ 3], decosahexaenoic acid [C22:  
6 $\omega$ 3], ricinoleic acid and derivatives thereof selected from the group consisting of the C1 to C6 alkyl esters thereof, the glycerol-poly-  
ethylene glycol esters thereof and the reaction product of hydrogenated natural oils composed largely of ricinoleic acid based oils,  
such as castor oil with ethylene oxide.



## ENHANCEMENT OF THE ACTION OF ANTI-INFECTIVE AGENTS

### FIELD OF THE INVENTION

This invention relates to pharmaceutical preparations (which expression is herein intended to include veterinary preparations) for use in combating  
5 infective organisms afflicting the animal body (which expression is herein intended to include the human body).

### BACKGROUND TO THE INVENTION

In EP **93912877.3** and **US patent 5,633,284** and their equivalents the  
10 applicant disclosed that dermatological or topical compositions comprising the combination of nitrous oxide [N<sub>2</sub>O] and at least one fatty acid, or lower alkyl ester thereof in a dermatologically acceptable carrier medium are useful in the treatment of a variety of skin, muscle and joint disorders. It also disclosed therein that such combinations may  
15 beneficially also include additional active ingredients.

Known anti-bacterial, anti-viral or anti-fungal agents were not amongst the active ingredients specifically mentioned in the patents but mention was made therein that coal tar solution (also known as Liquor Picis  
20 Carbonis) may be used as a supplementary active ingredient and that the resultant preparation is suitable for use in the treatment of, *inter alia* fever blisters, herpes simplex, shingles and chicken pox. While all of these conditions are caused by viral infections, the disclosures in these patents do not refer to that fact.

25 It is also disclosed in these patents that, in addition to the coal tar solution the composition may also contain an H1-antagonist antihistamine (e.g. diphenhydramine hydrochloride) and may in that form be used in the treatment of atopic and allergic conditions manifesting in skin irritations such as eczema, dermatitis and ringworm. The latter of these  
30 conditions is caused by a fungal infection. Again the disclosures in issue do not refer specifically to that fact.

It further disclosed an alternative composition in which the coal tar  
35 solution formulation is further provided with collagen and lanolin and this formulation was found to be useful in the treatment of persons suffering from acne vulgaris. Bacteria are involved in the condition but no mention was made of such involvement in those patents.



Since coal tar solution is in itself not known to be an anti-viral, anti-fungal or antibacterial agent, and has merely been mentioned as being weakly antiseptic, the aforementioned disclosures would not have been understood as suggesting that the nitrous oxide and fatty acid combination has any beneficial effect on the anti-viral or anti-fungal or anti-bacterial activity of any recognised anti-viral or anti-fungal or antibacterial agent or to have disclosed that such properties are displayed by coal tar solution. As will appear below the enhancement of the antibacterial, anti-fungal or anti-viral properties of known agents lie at the very heart of this invention.

Within the context of the disclosure in the abovementioned patent family the notional addressee most likely would, as did the inventor, have understood the role of the coal tar solution to sooth the itching and to assist in the repairing and healing of the skin which was damaged as a result of the infections/conditions in issue.

In **WO97/17978** and **US Patent 6,221,377** and in corresponding patents and pending patent applications in other jurisdictions the present applicant disclosed that the action of analgesic, anti-inflammatory and anti-pyretic drugs may be enhanced by administering such drugs in conjunction with a medium which comprises nitrous oxide and at least one long chain fatty acid selected from the group consisting of oleic acid, linoleic acid, alpha-linolenic acid, gamma linolenic acid, arachidonic acid, and any of the C<sub>1</sub> to C<sub>6</sub> alkyl esters of such long chain fatty acids, mixtures of such acids and mixtures of such esters. The medium may comprise the mixture known as Vitamin F Ethyl Ester and may optionally further comprise eicosapentaenoic acid [C20: 5 $\omega$ 3] and decosahexaenoic acid [C22: 6 $\omega$ 3].

It has now surprisingly been found that the aforesaid medium and media related thereto has the ability remarkably to enhance the action of known anti-infective agents. The expression "anti-infective agents" as used herein is intended to have its extended meaning and to include the antimicrobial agents, the anthelmintic agents and the anti-ectoparasitic agents, but to exclude coal tar solution and H1-antagonist antihistamines.

The exclusion of coal tar solution and H1-antagonist antihistamines from the ambit of the present invention is introduced without thereby conceding that the aforementioned patents and applications contain any disclosure of any anti-infective agent properties of such excluded



compounds, or that such properties are obvious in the light of the disclosures in such patents or applications. Such inferences are specifically denied. The exclusion is introduced simply to avoid what is anticipated to be a potential obstacle to the grant of a patent in respect of an insignificant part of potential subject matter which part in itself is not considered worth contesting during examination as it might unduly delay the implementation in practice of the significant features of the present invention. It is expected that the remaining bulk of the subject matter of the present invention will greatly contribute to the accessibility of medicines for the treatment of a large range of infections, including secondary infections in HIV-compromised patients, at significantly reduced costs.

The expressions "anthelmintic agents" and "anti-ectoparasitic" agents are further intended to cover both agents which serve to destroy and those which serve to inhibit the proliferation of helminths or ecto-parasites. Those expressions are hence also intended to be understood in the wider sense of these terms. The expression "antimicrobial agents" is similarly intended to be understood in the wider sense of that word and hence to have the meaning ascribed thereto in The McGraw-Hill Dictionary of Scientific and Technical Terms 2<sup>nd</sup> Ed 1978, namely all chemical compounds that either destroy or inhibit the growth of microscopic and sub microscopic organisms. This term is further specifically intended to include all the compounds falling within the Pharmacological Classification 20 set out as part of Regulation 5(1) of the General Regulations made in terms of the South African Medicines and Related Substances Control Act, Act 101 of 1965, as well as the active ingredients of all products falling within class 18 of the pharmacological classification employed in the Monthly Index of Medical Specialities ("MIMS") published by Times Media in South Africa. It is thus intended to include:

the anti-bacterial agents (including both antibiotics and substances other than antibiotics such as the sulfonamides, the erythromycins and other macrolides, the aminoglycosides, the tetracyclines, the chloramphenicols and the quinolones);  
the anti-fungal agents;  
the anti-viral agents (including anti-retroviral agents);  
the anti-protozoal agents;  
the tuberculostatics;  
the anti-leprotics;  
the germicides;  
and



the spirochaeticides.

The surprising finding of enhancement of action of the anti-infective agents referred to above is made against the background of the fact that there appears to be no earlier suggestion in the literature to the effect that either nitrous oxide or the long chain fatty acids used in the formulation referred to above, and hence also not the combination of these, has any effect whatsoever on the sensitivity of any micro-organism to any anti-infective agent.

The present invention is specifically, though not exclusively aimed at the enhancement of the action of anti-mycobacterial agents, and particularly those used in the treatment of patients infected with *Mycobacterium tuberculosis* (M.Tb.). This organism is one of the most significant human pathogens. It is responsible for an estimated seven million new cases of tuberculosis annually, and an estimated three million deaths worldwide. Of particular concern is the emergence of tuberculosis (TB) as an increasing cause of morbidity and mortality among persons compromised by human immune-deficiency virus (HIV) infection.

Although the prevalence of tuberculosis in developed countries declined in the first few decades of the 1900's, this trend has reversed and an increased incidence of tuberculosis has been reported in many countries. Africa alone is estimated to have approximately 170 million TB patients. In South Africa the incidence of tuberculosis is also rising and is at different levels in different population groups. The chapter on Tuberculosis in the 1999 edition of **South African Health Review** (available at <http://www.hst.org.za/sahr/>) opens with the shocking statement that: "*Despite the availability of effective and affordable treatment, the number of South Africans dying from tuberculosis continues to increase*". It is echoed by the summary of the startling overview in which it is recorded that "*A reported incidence of 254 cases per 100 000 for the period 1996 - 1998 combined with low cure rates, indicate that the epidemic is still out of control. Rising levels of HIV infection and multi-drug resistant TB (MDR TB) represent additional threats to TB control efforts.*" The number of reported cases of pulmonary TB (PTB) is reported in the Review to have risen from 90628 to 110016 new reported cases per year over the period 1996 to 1998, the estimated report rate having increased over the same period from 64% to 71%. Some of the provinces in South Africa contributed significantly to the national average TB incidence figure of 254 referred to above. The quoted Review reflects the figure for Eastern Cape as 388, for the



Northern Cape as 360, the Free State as 338 and the Western Cape as about 500 per 100000, almost double the national average. It has been reported elsewhere that the highest incidence of TB in the country is found in certain communities in the Western Cape where the estimated incidence is as high as 1400 per 100000.

Re-infection of patients is an ever-increasing problem and has been shown to be a function of reactivation of TB in patients not completing their therapy. It is also often associated with the appearance of drug resistant M.Tb. in the patient. The exact mechanism whereby drug resistance develops in mycobacteria is not yet fully understood, but the economic consequences thereof are a reality. The occurrence of drug resistant strains of M.Tb., generally known as multi-drug resistant Tuberculosis ("MDR TB") is also referred to in the aforementioned **South African Health Review 1999**. It states: *"Accurate figures for MDR TB are currently not available but surveys in three provinces (Western Cape, Mpumalanga and Gauteng) indicate a rate of 1% in new MDR TB cases, 4% in retreatment cases. This translates to at least 2 000 newly active cases of MDR TB in South Africa each year. MDR TB is extremely expensive to treat - R25 000 to R30 000 per patient for the drugs alone as opposed to less than R200 for a new patient with ordinary TB. Such patients generally also require to be hospitalised for long periods of time (usually between six and eighteen months), adding significantly to the cost of their treatment"*

In an attempt to reduce discontinuance of TB-treatments which has been implicated in reinfections and the development of resistant strains, the practice of directly observed treatment or DOTS has been resorted to, with some, but based on the foregoing quotes, not complete success.

Iron, heavy metals, and excessive alcohol consumption (an inherent feature of some identified high incidence TB communities) generate harmful reactive oxygen species which have been shown to be involved in the auto-oxidation of Rifampicin, an antibiotic anti-mycobacterial agent used in the treatment of tuberculosis, thereby generating more radical species. These free radicals have been implicated in the liver toxicity experienced with use of Rifampicin.

These problems associated with TB have led to the investigations associated with the present invention.



It was pointed out in WO97/17978 referred to above that nitrous oxide is a natural gas which is also produced synthetically, and also known by the trivial name "laughing gas" which has been in use for many years as an inhalation anaesthetic and analgesic, particularly in dentistry.

5 It was further stated that nitrous oxide has been reported to have a synergistic or potentiating effect on halothane and other gaseous anaesthetics [See Goodman & Gilman's **The Pharmacological Basis of Therapeutics** 8th Ed. 1990 pp. 298-300].

10 Since such known synergism or potentiation is based on the use of nitrous oxide administered by inhalation, and since the use of nitrous oxide on its own as an anaesthetic and analgesic has likewise been in the form of an inhalation agent, the use of nitrous oxide for all these purposes have been  
15 confined to hospitalised patients or, at best, to treatments carried out by medical practitioners in their consulting rooms, or treatments carried out by or under supervision of a nurse in charge of a home-care patient.

20 Nitrous oxide is known to be soluble in water and it has been reported that at 20°C and 2 atm pressure one litre of the gas dissolves in 1,5 litres of water, see The Merck Index 10th Ed. p. 6499.

25 Nitrous oxide is also known for its use as a propellant gas, mainly as a substitute for propellant gases such as chlorofluorocarbons, and more particularly to produce a food product mousse such as whipped cream or chocolate mousse or quick-breaking foams for hair treatment preparations. See in this regard U.K. Patent 1033299, U.K. Patent 1105919 and European Patent Application EPA-0123827. None of these  
30 prior publications suggests that the nitrous oxide gas plays any other role than a physical one, i.e. to expand on being depressurised and thereby to create a mousse or foam. In fact it is typically regarded as an inert in these applications and useful due to the fact that it is colourless, odourless and tasteless but soluble in water and oils.

35 There appears to be no suggestion in the literature, other than the applicants own prior patents and patent applications referred to above, that aqueous solutions of nitrous oxide might have any effect on man or animals. As far as the present applicant knows, it has also never been suggested that nitrous oxide may be used in conjunction with any anti-  
40 infective agent to enhance the known action of such agent.



It is known in the pharmaceutical field to formulate active ingredients in so-called liposomal formulations. Unlike the present invention which is based on formulations containing long chain fatty acids and esters thereof the liposomes are based on a clearly distinguishable group of compounds  
5 namely the phospholipids, and generally also contain cholesterol as a stabilising agent and may further contain liolecitein. These compounds or classes form no part of the present invention and, in case it is necessary to do so, are specifically excluded from the group of long chain fatty acids and derivatives thereof incorporated in the method or formulation of the  
10 invention.

### OBJECT OF THE INVENTION

It is an object of the present invention to provide a method of enhancing the known action of anti-infective agents and to provide pharmaceutical  
15 preparations of such anti-infective agents which preparations have enhanced action compared to the action of known formulations containing the same agents.

These objects stem from the observations made by present applicant in respect of a selection of agents falling within the group of anti-infective  
20 agents as herein defined, which can advantageously be formulated with nitrous oxide and an oil based on long chain fatty acids disclosed herein, to elicit a more potent response, for each agent according to its own inherent properties, or to evoke such response more rapidly than it does  
25 when used by conventional administration of the agent in issue.

### STATEMENTS OF THE INVENTION

According to the present invention there is provided a method of enhancing the action of an anti-infective agent characterised in that the  
30 agent is selected from the group comprising antimicrobial agents, the anthelmintic agents and the anti-ectoparasitic agents, but excluding coal tar solution and H1-antagonist antihistamines, comprising the step of formulating the agent with an administration medium which comprises a solution of nitrous oxide gas in a pharmaceutically acceptable carrier solvent for the  
35 gas and which administration medium includes at least one fatty acid or ester or other suitable derivative thereof selected from the group consisting of oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, arachidonic acid, eicosapentaenoic acid [C20: 5 $\omega$ 3], docosahexaenoic acid [C22: 6 $\omega$ 3], ricinoleic acid and derivatives thereof  
40 selected from the group consisting of the C1 to C6 alkyl esters thereof, the glycerol-polyethylene glycol esters thereof and the reaction product of



hydrogenated natural oils composed largely of ricinoleic acid based oils, such as castor oil with ethylene oxide.

5 According to a further aspect of the present invention there is provided a pharmaceutical preparation comprising an anti-infective agent characterised in that it is selected from the group comprising antimicrobial agents, the anthelmintic agents and the anti-ectoparasitic agents, but excluding coal tar solution and H1-antagonist antihistamines, which agent is formulated with an administration medium which comprises a  
10 solution of nitrous oxide in a pharmaceutically acceptable carrier solvent for the gas and which includes at least one fatty acid or ester or other suitable derivative thereof selected from the group consisting of oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, arachidonic acid, eicosapentaenoic acid [C20: 5 $\omega$ 3], decosahexaenoic acid [C22:  
15 6 $\omega$ 3], ricinoleic acid and the derivatives thereof selected from the group consisting of the C1 to C6 alkyl esters thereof, the glycerol-polyethylene glycol esters thereof and the reaction product of hydrogenated natural oils composed largely of ricinoleic acid based oils, such as castor oil, with ethylene oxide.

20 The administration medium preferably includes the eicosapentaenoic acid [C20: 5 $\omega$ 3] and/or decosahexaenoic acid [C22: 6 $\omega$ 3] as additional long chain fatty acids to at least one of the other components of the carrier medium defined above.

25 The reaction product of hydrogenated natural oils composed largely of ricinoleic acid based oils with ethylene oxide is preferably produced from castor oil of which the fatty acid content is known to be predominantly composed of ricinoleic acid. This product is known as PEG-n-Hydrogenated  
30 Castor Oil. A range of such products is marketed by BASF under the trade description of Cremophor RH grades. Glycerol-polyethylene glycol ester of ricinoleic acid is also marketed by the same company but under the trade description of Cremophor EL.

35 The carrier solvent for the nitrous oxide gas may be water or any of the pharmaceutically acceptable alcohols, ethers, oils or polymers such as a polyethylene glycol or the like. The oil may be organic or mineral oil. The organic oil may be an essential oil based on long chain fatty acids having between 14 and 22 carbon atoms in the fatty acid. The oil may also be of  
40 either natural or synthetic origin and, if of natural origin, it may be either plant oil or animal oil. As plant oils those rich in gamma linolenic acid



[GLA] are preferred and as animal oil dairy cream may be used.

In the preferred form of the invention the solution is an aqueous solution saturated with nitrous oxide. Preferably the water is deionised and purified to be free of microbes.

When the formulation containing the anti-infective agent to be enhanced by means of the nitrous oxide is to be in a liquid (including an encapsulated liquid) presentation for oral administration or in a nasal or bronchial or pulmonary spray or in the form of an injectable formulation, such formulation may incorporate, as part of the administration medium, water or acceptable other liquid into which the nitrous oxide is dissolved and in which the fatty acid or ester thereof is either dissolved or suspended or emulsified along with the anti-infective agent to be enhanced by being formulated therewith.

Likewise, where the anti-infective agent is to be administered to the patient as a topical, buccal or vaginal cream or ointment, or as a suppository, the formulation used in making up such cream, ointment, or suppository may incorporate, along with the anti-infective agent to be enhanced, a quantity of water or other liquid containing, and preferably saturated with, nitrous oxide, the long chain fatty acid or ester thereof and the anti-infective agent formulated therewith, and, further, such additional excipients and carriers as are conventionally used in the pharmaceutical trade in making up such dosage forms.

The carrier solvent for the nitrous oxide gas may thus in an alternative formulation according to the invention be essentially non-aqueous and composed of least one fatty acid or ester thereof selected from the group consisting of oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, arachidonic acid, eicosapentaenoic acid [C20: 5 $\omega$ 3], decosahexaenoic acid [C22: 6 $\omega$ 3], ricinoleic acid and derivatives thereof selected from the group consisting of the C1 to C6 alkyl esters thereof, the glycerol-polyethylene glycol esters thereof and the reaction product of hydrogenated natural oils composed largely of ricinoleic acid based oils with ethylene oxide, required to be part of the formulation.

A formulation suited to transdermal application whether as an ointment, cream or lotion or in the form of a skin patch providing a reservoir for the formulation is also a preferred form of the formulation according to the invention.



The essential fatty acid, or ester thereof, component of the composition preferably comprises a mixture of esters of the fatty acids listed above. Thus, in the most preferred form of the invention the fatty acid component of the composition is constituted by the complex known as Vitamin F and in this regard it is preferred to make use of the ester form of Vitamin F known as Vitamin F Ethyl Ester. This product is commercially available under the trade description of Vitamin F Ethyl Ester CLR 110 000 Sh.L. U./g from CLR Chemicals Laboratorium Dr.Kurt Richter GmbH of Berlin, Germany. The typical fatty acid distribution of this product is as follows:

< C<sub>16</sub> : 0  
C<sub>16.0</sub> : 8,3 %  
C<sub>18.0</sub> : 3,5 %  
15 C<sub>18.1</sub> : 21,7 %  
C<sub>18.2</sub> : 34,8 %  
C<sub>18.4</sub> : 28,0 %  
> C<sub>18</sub> : 1,6 %  
unknown: 2,1 %

20 It is further preferred to add to the formulation the long chain fatty acids known as eicosapentaenoic acid [C20:5 $\omega$ 3] and decosahexaenoic acid [C22:6 $\omega$ 3]. Such a product combination is available from Roche Lipid Technology under the trade name "Ropufa '30' n-3 oil".

25 It has been found by microscopic studies that the formulation of the anti-infective agents with a medium as herein described gives rise to the formation of minute, generally spherical bodies, within which, or attached to which the active ingredient is contained in a stable form and from which it is delivered at the site of action namely on or inside the infective agent.

30 The anti-infective agent utilised in the method or formulation according to the present invention may comprise any one or more of the vast spectrum of anti-infective agents as herein defined.

35 In a preferred form of the invention the anti-infective agent is selected from the group comprising:

40 the anthelmintics  
the anti-ectoparasitcides



the anti-bacterial agents (including both antibiotics and substances other than antibiotics);  
the antifungal agents;  
the anti-viral agents;  
5 the anti-protozoal agents;  
the tuberculostatics;  
the anti-leprotics;  
the germicides;  
and  
10 the spirochaetocides.

From amongst these anti-infective agents this invention is particularly concerned with the anti-bacterials and the tuberculostatics. These classes of agents overlap to some extent.

15 The anti-infective agent may in a specific application of the invention comprise an antimicrobial of the class of compounds known as the tuberculostatics or anti-mycobacterial compounds and may specifically be selected from the group consisting of Rifampicin, Isoniazid, Pyrazinamide,  
20 Ethambutol and combinations of any two or more of these.

It is a further aspect of the invention that the formulation, and specifically, though not exclusively, the anti-TB formulation of the invention, may be prepared to be adapted for pulmonary administration.  
25 In the case of the anti-TB formulation it will thereby bring the formulation into contact with the pathogen at a primary locus thereof and without passage through, or absorption from the digestive tract and possible subsequent passage through the liver.

30 The invention has not yet been demonstrated by empirical work to be applicable to all the agents listed below. However in respect of such anti-infective agents which have already been formulated with the aforementioned administration medium of the invention, and evaluated by different methods for the anticipated enhancement of anti-infective  
35 action, no negative result has as yet been seen despite the chemical diversity of the anti-infective agents which has been investigated. The applicant thus confidently expects, on the basis of the observations in respect of products representing a range of classes of such agents, that the invention will find general application across the entire spectrum of  
40 anti-infective agents embraced by the term as herein defined and of which some examples are set out below. It is part of the applicant's present postulations by which it seeks to find an understanding of the



invention and to which it does not wish to be bound at this stage, that while the administration medium of the present invention serves to transport the anti-infective agent formulated therewith most efficiently through the human or animal body, that medium also plays an important role in transferring, by an as yet unexplained mechanism, the anti-infective agent through the outer membranes of and into the pathogenic organism thereby to cause an effective anti-infective dose of the agent rapidly to be achieved and to be maintained in the organism until it finally succumbs to the effect of the anti-infective agent.

It is in this respect that the applicant believes that the present invention will find general application despite the vast list of agents mentioned below. The following table sets out examples of the specific anti-infective agents with which this invention is concerned will now be identified with reference to the broad classes in which they fall and, in some cases, also with reference the respective indications for which such agents are indicated and, in some cases, further also with reference to the infective agent giving rise to the indication to be addressed which products comprise the following:

#### A. SULPHONAMIDES

- 1) Short-acting
  - SULPHAPYRIDINE-
    - 1) Inflammatory bowel diseases and in rheumatoid arthritis
  - SULPHADIAZINE-
    - 1) Nocardiosis (Nocardia species)
    - 2) Toxoplasmosis + Pyrimethamine
    - 3) Long term prophylaxis of rheumatic fever
  - SULPHADIMIDINE-
  - SULPHAFURAZOLE-
- 2) Medium-acting:
  - SULPHAMETHOXAZOLE -
- 3) Long-acting:
  - SULPHADIMETHOXINE -
  - SULPHAMETHOXYDIAZINE-
  - SULPHAMETHOXYPYRIDAZINE-
- 4) Ultra-Long-acting:
  - SULFADOXINE-



- 5) SULFAMETOPYRAZINE-  
Topical sulphonamide:  
SILVER SULPHADIAZINE-  
1) Antibacterial in patients with burns
- 5 MAFENIDE ACETATE-  
1) Antibacterial in patients with burns  
SULPHACETAMIDE-  
6) Other sulphonamides:  
SULPHAGUANIDINE-  
10 1) Gastrointestinal infections  
SULPHASALAZINE-  
1) Inflammatory bowel diseases and in rheumatoid arthritis  
SUCCINYLSULPHATHIAZOLE-  
1) Gastrointestinal infections  
15 PHTHALYLSULPHATHIAZOLE-  
1) Gastrointestinal infections  
7) SULPHONAMIDE COMBINATIONS:  
CO-TRIMOXAZOLE (Trimethoprim+ Sulphamethoxazole)-  
20 1) Abscesses, Bacteremia, Endocarditis, Pneumonia,  
Osteomyelitis, Cellulitis and other diseases that are  
Methicillin-sensitive (*Staphylococcus aureus*)  
2) Pneumonia, Arthritis, Sinusitis, Otitis that are Penicillin-  
sensitive (*Streptococcus Pneumoniae*)  
3) Meningitis and Bacteremia (*Listeria monocytogenes*)  
25 4) Urinary tract infections, Bacteremia, Other infections  
(*Escherichia coli*)  
5) Urinary tract and other infections (*Enterobacter* species)  
6) Typhoid fever, Paratyphoid fever, Bacteremia, Acute  
gastroenteritis (*Salmonella*)  
30 7) Acute gastro-enteritis (*Shigella*)  
8) Otitis media, Sinusitis, Pneumonia, Epiglottitis, Meningitis  
(*Haemophilus influenzae*)  
9) Chancroid (*Haemophilus ducreyi*)  
10) Brucellosis (*Brucella*) ± Gentamicin  
35 11) Yersiniosis (*Yersinia enterocolitica*)  
12) Cholera (*Vibrio cholerae*)  
13) Meningitis (*Flavobacterium meningosepticum*)  
14) Melioidosis (*Pseudomonas pseudomallei*)



ENOXACIN

LOMEFLOXACIN

PEFLOXACIN

AMIFLOXACIN

5 FLEROXACIN

LEVOFLOXACIN

NADIFLOXACIN

RUFLOXACIN

10 SPARFLOXACIN

1) Active against Streptococcus pneumoniae and anaerobic bacteria.

TOSUFLOXACIN

ENROFLOXACIN

15 **C. Anti-Septic and Analgesic Agents for Urinary Tract Infections**

METHENAMIN

1) Not a primary drug for the treatment of acute urinary tract infections, but it is of value for chronic suppressive treatment.

20 NITROFURANTOIN

1) Urinary tract infection (Escherichia coli)

MENAZOPYRIDINE

25 1) Is not a urinary antiseptic but it does have an analgesic action on the urinary tract and alleviates symptoms of dysuria, frequency, burning and urgency.

**D. PENICILLIN**

NARROW SPECTRUM

BENZYL PENICILLIN (Penicillin G) [acid-labile]



- 1) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome and Other systemic infections (*Streptococcus pyogenes* [Group A])
- 5 2) Endocarditis, Bacteremia (*Streptococcus* [viridans group]) ± Gentamicin.
- 3) Bacteremia, Endocarditis, Meningitis. (*Streptococcus agalactiae* [Group B]) ± Aminoglycoside.
- 10 4) Bacteremia, Endocarditis, Brain and other abscesses, Sinusitis (*Streptococcus* [anaerobic species])
- 5) Pneumonia, Arthritis, Sinusitis, Otitis [Penicillin – Sensitive and Penicillin – Resistant] Endocarditis, Meningitis, other serious infections [Penicillin – Sensitive] (*Streptococcus pneumoniae* [pneumococcus])
- 15 6) Endocarditis or other serious infections (bacteremia), Urinary tract infections (*Enterococcus*) + Gentamicin
- 7) Penicillin – sensitive gonococcus (*Neisseria gonorrhoeae*) + Probenecid.
- 20 8) Meningitis (*Neisseria meningitidis* [meningococcus])
- 9) "Malignant pustule", Pneumonia (*Bacillus anthracis*)
- 10) Endocarditis, Infected foreign bodies, Bacteremia (*Corynebacterium* species, aerobic and anaerobic [diphtheroids]) ± an Aminoglycoside or + Rifampin
- 25 11) Meningitis, Bacteremia (*Listeria monocytogenes*) ± Gentamicin
- 12) Erysipeloid (*Erysipelothrix rhusiopathiae*)
- 13) Gas gangrene (*Clostridium perfringens* and other species)
- 14) Tetanus (*Clostridium tetani*)
- 30 15) Urinary tract infection, Bacteremia, Other infections (*Escherichia coli*) + a Penicillinase inhibitor.
- 16) Urinary tract and other infections (*Proteus*, other species) + a  $\beta$  – Lactamase inhibitor
- 17) Wound infection (animal bites), Abscesses, Bacteremia, Meningitis (*Pasteurella multocida*)
- 35 18) Ulcerative pharyngitis, Lung abscess, Empyema, Genital infections, Gingivitis (*Fusobacterium nucleatum*)
- 19) Bacteremia, Arthritis, Endocarditis, Abscesses (*Streptobacillus moniliformis*)
- 20) Syphilis (*Treponema pallidum*)
- 40 21) Yaws (*Treponema pertenue*)
- 22) Stage 2 – neurological, Cardiac, Arthritis (*Borrelia burgdorferi* [Lyme disease])
- 23) Relapsing fever (*Borrelia recurrentis*)



- 24) Weil's disease, Meningitis (*Leptospira*)
- 25) Cervicofacial, Abdominal, Thoracic, and other lesions (*Actinomyces israelii*)

## PHENOXYMETHYL-PENICILLIN

5 (Penicillin V)

[acid – stable]

- 10 1) Pharyngitis, Scarlet Fever, Otitis Media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome, and other systemic infections (*Streptococcus pyogenes* [Group A])
- 15 2) Pneumonia, Arthritis, Sinusitis, Otitis [Penicillin – Sensitive and Penicillin – Resistant] Endocarditis, Meningitis, other serious infections [Penicillin –sensitive] (*Streptococcus pneumoniae* [*pneumococcus*])
- 3) Urinary tract infections (*Enterococcus*)
- 4) Urinary tract infection, Bacteremia, Other infections (*Escherichia coli*) + a Penicillinase-inhibitor.
- 20 5) Urinary tract and other infections (*Proteus*, other species) + a  $\beta$  – Lactamase inhibitor

**E. PENICILLIN**

## BROAD SPECTRUM

25 AMOXICILLIN

- 30 1) Pharyngitis, Scarlet Fever, Otitis Media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome and other systemic infections (*Streptococcus pyogenes* [group A])
- 2) Pneumonia, Arthritis, Sinusitis, Otitis [Penicillin – Sensitive and Penicillin – Resistant] (*Streptococcus pneumoniae* [*Pneumococcus*])
- 3) Urinary tract and other Infections (*Proteus mirabilis*)
- 35 4) Otitis Media, Sinusitis, Pneumonia (*Haemophilus influenzae*) + Clavulanic acid.
- 5) Wound – infection (animal bites), Abscesses, Bacteremia, Meningitis (*Pasteurella multocida*) + Clavulanic acid
- 6) Erythema chronica migrans – skin (*Borrelia burgdorferi* [Lyme disease])



- 5                   7) Pulmonary lesions, Brain abscess, Lesions of other organs  
(*Nocardia asteroides*) + Clavulanic acid
- 8) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*) +  
Clavulanic acid
- 9) Penicillin – Sensitive gonococcus (*Neisseria gonorrhoeae*)  
+ Probenecid

**AMPICILLIN**

- 10               1) Bacteremia, Endocarditis, Meningitis (*Streptococcus*  
*agalactiae* [Group B])
- 2) Urinary tract infection, Endocarditis, or Other serious  
infections [Bacteremia] (*Enterococcus*)
- 15               3) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*) +  
Clavulanic acid
- 4) Penicillin – Sensitive gonococcus (*Neisseria gonorrhoeae*)  
+ Probenecid
- 5) Meningitis, Bacteremia (*Listeria monocytogenes*)
- 20               6) Urinary tract infection, Other infections, Bacteremia  
(*Escherichia coli*) + an Aminoglycoside
- 7) Endocarditis, Infected foreign bodies, Bacteremia  
(*Corynebacterium* species, aerobic and anaerobic  
[diphtheroids]) + Sulbactam
- 8) Urinary tract and other infections (*Proteus mirabilis*)
- 25               9) Typhoid Fever, Paratyphoid Fever, Bacteremia, Acute  
Gastroenteritis (*Salmonella*)
- 10) Acute Gastroenteritis (*Shigella*)
- 11) Epiglottitis, Meningitis (*Haemophilus influenza*) +  
Sulbactam
- 30               12) Bacteremia, Endocarditis, Meningitis (*Campylobacter*  
*fetus*)
- 13) Cervicofacial, Abdominal, Thoracic, an Other lesions  
(*Actinomyces israelii*)

35               **TICARCILLIN**

- 1) Urinary tract and other infections (*Enterobacter* species)
- 2) Pneumonia, Bacteremia (*Pseudomonas aeruginosa*) ± an  
Aminoglycoside
- 3) Urinary tract infection (*Pseudomonas aeruginosa*)
- 40               4) Variety of nosocomial and opportunistic infections  
(*Serratia*) + an Aminoglycoside

**PIPERACILLIN**



- 5
- 1) Urinary tract and other infections (Enterobacter species)
  - 2) Pneumonia, Bacteremia (Pseudomonas aeruginosa) ± an Aminoglycoside
  - 3) Urinary tract infection (Pseudomonas aeruginosa)
  - 4) Variety of nosocomial and opportunistic infections (Serratia) + an Aminoglycoside

**MEZLOCILLIN**

- 10
- 1) Urinary tract and other infections (Enterobacter species)
  - 2) Pneumonia, Bacteremia (Pseudomonas aeruginosa) ± an Aminoglycoside
  - 3) Urinary tract infection (Pseudomonas aeruginosa)
  - 15 4) Variety of nosocomial and opportunistic infections (Serratia) + an Aminoglycoside

**AZLOCILLIN**

- 20
- 1) Urinary tract and Other infections (Enterobacter species)
  - 2) Pneumonia, Bacteremia (Pseudomonas aeruginosa) ± an Aminoglycoside
  - 3) Urinary tract infection (Pseudomonas aeruginosa)
  - 4) Variety of nosocomial and opportunistic infections (Serratia) + an Amihoglycoside



BACAMPICILLIN  
TALAMPICILLIN

PIVAMPICILLIN

CARBENICILLIN  
APALCILLIN  
CARINDACILLIN  
PIVMECILLINAM  
CARFECILLIN

METAAMPICILLIN

HETACILLIN

TEMOCILLIN

**F. PENICILLIN**

PENICILLINASE – RESISTANT PENICILLINS (isoxazoly penicillins)

OXACILLIN

- 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis, and Other Staphylococcus aureus infections [methicillin – sensitive] (Staphylococcus aureus)

CLOXACILLIN

- 1) Effective against Penicillinase – Producing Staphylococcus aureus

DICLOXACILLIN

- 1) Effective against Penicillinase – Producing Staphylococcus aureus

FLUCLOXACILLIN

- 1) Effective against Penicillinase – Producing Staphylococcus aureus

METHICILLIN

- 1) Effective against Penicillinase – Producing Staphylococcus aureus



## NAFCILLIN

- 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis, and Other Staphylococcus aureus infections [methicillin-sensitive] (Staphylococcus aureus)

5 **G. CEPHALOSPORINS**

## G1. FIRST GENERATION

## CEPHAZOLIN / CEPHRADINE

- 10 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis and other Staphylococcus aureus infections [Methicillin – Sensitive] (Staphylococcus aureus)
- 15 2) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome and other systemic infections (Streptococcus pyogenes [Group A])
- 20 3) Bacteremia, Endocarditis (Streptococcus agalactiae [Group B])
- 4) Bacteremia, Endocarditis, Brain and other abscesses, Sinusitis (Streptococcus [anaerobic species])
- 25 5) Pneumonia, Arthritis, Sinusitis, Otitis media [Penicillin – Sensitive] (Streptococcus Pneumoniae [Pneumococcus])
- 6) Urinary tract infection, other infections, Bacteremia (Escherichia coli)
- 7) Urinary tract and other infections (Proteus mirabilis)
- 8) Urinary tract infection (Klebsiella pneumoniae)
- 9) Pneumonia (Klebsiella pneumoniae) ± an Aminoglycoside
- 30 10) Wound infection (animal bite), Abscesses, Bacteremia, Meningitis (Pasteurella Multiocida)
- 11) Ulcerative pharyngitis, Lung abscess, Empyema, Genital infections, Gingivitis (Fusobacterium nucleatum)
- 12) "Malignant Pustule" Pneumonia (Bacillus anthracis)

## CEPHALORIDINE

- 35 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis and other Staphylococcus aureus infections [Methicillin – Sensitive] (Staphylococcus aureus)
- 40 2) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome and other systemic infections (Streptococcus pyogenes [Group A])



- 3) Bacteremia, Endocarditis (*Streptococcus agalactiae* [Group B])
- 4) Bacteremia, Endocarditis, Brain and other abscesses, Sinusitis (*Streptococcus* [anaerobic species])
- 5) Pneumonia, Arthritis, Sinusitis, Otitis media [Penicillin – Sensitive] (*Streptococcus Pneumoniae* [*Pneumococcus*])
- 6) Urinary tract infection, other infections, Bacteremia (*Escherichia coli*)
- 7) Urinary tract and other infections (*Proteus mirabilis*)
- 8) Urinary tract infection (*Klebsiella pneumoniae*)
- 9) Pneumonia (*Klebsiella pneumoniae*) ± an Aminoglycoside
- 10) Wound infection (animal bite), Abscesses, Bacteremia, Meningitis (*Pasteurella Multiocida*)
- 11) Ulcerative pharyngitis, Lung abscess, Empyema, Genital infections, Gingivitis (*Fusobacterium nucleatum*)
- 12) "Malignant Pustule" Pneumonia (*Bacillus anthracis*)

## CEPHRADINE

- 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis and other *Staphylococcus aureus* infections [Methicillin – Sensitive] (*Staphylococcus aureus*)
- 2) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome and other systemic infections (*Streptococcus pyogenes* [Group A])
- 3) Bacteremia, Endocarditis (*Streptococcus agalactiae* [Group B])
- 4) Bacteremia, Endocarditis, Brain and other abscesses, Sinusitis (*Streptococcus* [anaerobic species])
- 5) Pneumonia, Arthritis, Sinusitis, Otitis media [Penicillin – Sensitive] (*Streptococcus Pneumoniae* [*Pneumococcus*])
- 6) Urinary tract infection, other infections, Bacteremia (*Escherichia coli*)
- 7) Urinary tract and other infections (*Proteus mirabilis*)
- 8) Urinary tract infection (*Klebsiella pneumoniae*)
- 9) Pneumonia (*Klebsiella pneumoniae*) ± an Aminoglycoside
- 10) Wound infection (animal bite), Abscesses, Bacteremia, Meningitis (*Pasteurella Multiocida*)
- 11) Ulcerative pharyngitis, Lung abscess, Empyema, Genital infections, Gingivitis (*Fusobacterium nucleatum*)
- 12) "Malignant Pustule" Pneumonia (*Bacillus anthracis*)



## CEFROXADINE

- 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis and other *Staphylococcus aureus* infections [Methicillin – Sensitive] (*Staphylococcus aureus*)
- 2) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome and other systemic infections (*Streptococcus pyogenes* [Group A])
- 3) Bacteremia, Endocarditis (*Streptococcus agalactiae* [Group B])
- 4) Bacteremia, Endocarditis, Brain and other abscesses, Sinusitis (*Streptococcus [anaerobic species]*)
- 5) Pneumonia, Arthritis, Sinusitis, Otitis media [Penicillin – Sensitive] (*Streptococcus Pneumoniae* [*Pneumococcus*])
- 6) Urinary tract infection, other infections, Bacteremia (*Escherichia coli*)
- 7) Urinary tract and other infections (*Proteus mirabilis*)
- 8) Urinary tract infection (*Klebsiella pneumoniae*)
- 9) Pneumonia (*Klebsiella pneumoniae*) ± an Aminoglycoside
- 10) Wound infection (animal bite), Abscesses, Bacteremia, Meningitis (*Pasteurella Multiocida*)
- 11) Ulcerative pharyngitis, Lung abscess, Empyema, Genital infections, Gingivitis (*Fusobacterium nucleatum*)
- 12) "Malignant Pustule" Pneumonia (*Bacillus anthracis*)

## CEFADROXIL

- 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis and other *Staphylococcus aureus* infections [Methicillin – Sensitive] (*Staphylococcus aureus*)
- 2) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome and other systemic infections (*Streptococcus pyogenes* [Group A])
- 3) Bacteremia, Endocarditis (*Streptococcus agalactiae* [Group B])
- 4) Bacteremia, Endocarditis, Brain and other abscesses, Sinusitis (*Streptococcus [anaerobic species]*)
- 5) Pneumonia, Arthritis, Sinusitis, Otitis media [Penicillin – Sensitive] (*Streptococcus Pneumoniae* [*Pneumococcus*])
- 6) Urinary tract infection, other infections, Bacteremia (*Escherichia coli*)



- 5
- 7) Urinary tract and other infections (*Proteus mirabilis*)
  - 8) Urinary tract infection (*Klebsiella pneumoniae*)
  - 9) Pneumonia (*Klebsiella pneumoniae*) ± an Aminoglycoside
  - 10) Wound infection (animal bite), Abscesses, Bacteremia, Meningitis (*Pasteurella Multocida*)
  - 11) Ulcerative pharyngitis, Lung abscess, Empyema, Genital infections, Gingivitis (*Fusobacterium nucleatum*)
  - 12) "Malignant Pustule" Pneumonia (*Bacillus anthracis*)

10 CETATRIAZINE

- 15
- 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis and other *Staphylococcus aureus* infections [Methicillin – Sensitive] (*Staphylococcus aureus*)
  - 2) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome and other systemic infections (*Streptococcus pyogenes* [Group A])
  - 20 3) Bacteremia, Endocarditis (*Streptococcus agalactiae* [Group B])
  - 4) Bacteremia, Endocarditis, Brain and other abscesses, Sinusitis (*Streptococcus* [anaerobic species])
  - 5) Pneumonia, Arthritis, Sinusitis, Otitis media [Penicillin – Sensitive] (*Streptococcus Pneumoniae* [*Pneumococcus*])
  - 25 6) Urinary tract infection, other infections, Bacteremia (*Escherichia coli*)
  - 7) Urinary tract and other infections (*Proteus mirabilis*)
  - 8) Urinary tract infection (*Klebsiella pneumoniae*)
  - 9) Pneumonia (*Klebsiella pneumoniae*) ± an Aminoglycoside
  - 30 10) Wound infection (animal bite), Abscesses, Bacteremia, Meningitis (*Pasteurella Multocida*)
  - 11) Ulcerative pharyngitis, Lung abscess, Empyema, Genital infections, Gingivitis (*Fusobacterium nucleatum*)
  - 12) "Malignant Pustule" Pneumonia (*Bacillus anthracis*)

35 CEFALEXIN

- 40
- 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis and other *Staphylococcus aureus* infections [Methicillin – Sensitive] (*Staphylococcus aureus*)
  - 2) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like



## 12) "Malignant Pustule" Pneumonia (Bacillus anthracis)

## CEFPROZIL

- 5 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis and other Staphylococcus aureus infections [Methicillin – Sensitive] (Staphylococcus aureus)
- 10 2) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome and other systemic infections (Streptococcus pyogenes [Group A])
- 15 3) Bacteremia, Endocarditis (Streptococcus agalactiae [Group B])
- 4) Bacteremia, Endocarditis, Brain and other abscesses, Sinusitis (Streptococcus [anaerobic species])
- 5) Pneumonia, Arthritis, Sinusitis, Otitis media [Penicillin – Sensitive] (Streptococcus Pneumoniae [Pneumococcus])
- 6) Urinary tract infection, other infections, Bacteremia (Escherichia coli)
- 20 7) Urinary tract and other infections (Proteus mirabilis)
- 8) Urinary tract infection (Klebsiella pneumoniae)
- 9) Pneumonia (Klebsiella pneumoniae) ± an Aminoglycoside
- 10) Wound infection (animal bite), Abscesses, Bacteremia, Meningitis (Pasteurella Multiocida)
- 25 11) Ulcerative pharyngitis, Lung abscess, Empyema, Genital infections, Gingivitis (Fusobacterium nucleatum)
- 12) "Malignant Pustule" Pneumonia (Bacillus anthracis)

**CEPHALOSPORINS**30 **G2 SECOND GENERATION**

## CEFOXITIN

- 1) Penicillin – Sensitive and Penicillinase – Producing gonococcus (Neisseria gonorrhoeae)
- 35 2) Gas gangrene (Clostridium perfringens and other species)
- 3) Variety of nosocomial and opportunistic infections
- 4) Ulcerative pharyngitis, Lung abscess, Empyema, Genital infections, Gingivitis (Fusobacterium nucleatum)

## CEFOTETAN

- 40 1) Gas gangrene (Clostridium perfringens and other species)
- 2) Variety of nosocomial and opportunistic infections

## CEFUROXIME AXETIL

- 1) Otitis media, Sinusitis, Pneumonia (Haemophilus influenza)



## CEPHAMANDOLE

- 5
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus mirabilis*)
  - 3) Urinary tract infection (*Klebsiella Pneumoniae*)
  - 4) Pneumonia (*Klebsiella Pneumoniae*)  $\pm$  an Aminoglycoside

## CEFUROXIME

- 10
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus mirabilis*)
  - 3) Urinary tract infection (*Klebsiella Pneumoniae*)
  - 4) Pneumonia (*Klebsiella Pneumoniae*)  $\pm$  an Aminoglycoside

## CEFONICID

- 15
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus mirabilis*)
  - 3) Urinary tract infection (*Klebsiella Pneumoniae*)
  - 4) Pneumonia (*Klebsiella Pneumoniae*)  $\pm$  an Aminoglycoside

## CEFORANIDE

- 20
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus mirabilis*)
  - 3) Urinary tract infection (*Klebsiella Pneumoniae*)
  - 4) Pneumonia (*Klebsiella Pneumoniae*)  $\pm$  an Aminoglycoside

## CEFOTIAM

- 25
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus mirabilis*)
  - 3) Urinary tract infection (*Klebsiella Pneumoniae*)
  - 4) Pneumonia (*Klebsiella Pneumoniae*)  $\pm$  an Aminoglycoside

## CEFAMYCINS

- 30
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus mirabilis*)
  - 3) Urinary tract infection (*Klebsiella Pneumoniae*)
  - 4) Pneumonia (*Klebsiella Pneumoniae*)  $\pm$  an Aminoglycoside

## CEFACLOR

- 35
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus mirabilis*)
  - 3) Urinary tract infection (*Klebsiella Pneumoniae*)
  - 4) Pneumonia (*Klebsiella Pneumoniae*)  $\pm$  an Aminoglycoside

## LORACARBEF

- 40
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus mirabilis*)
  - 3) Urinary tract infection (*Klebsiella Pneumoniae*)
  - 4) Pneumonia (*Klebsiella Pneumoniae*)  $\pm$  an Aminoglycoside



# **CEPHALOSPORINS** **G3 THIRD GENERATION**

## **CEFTRIAXONE**

- |    |   |
|----|---|
| 5  | 1) Endocarditis, Bacteremia (Streptococcus [Viridans Group])  |
|    | 2) Meningitis (Streptococcus agalactiae [Group B])  |
|    | 3) Pneumonia, Arthritis, Sinusitis, Otitis [Penicillin – Resistant] (Streptococcus pneumoniae [Pneumococcus])                                   |
| 10 | 4) Endocarditis, Meningitis, Other serious infections [Penicillin intermediate-resistant and Penicillin – Sensitive] (Streptococcus Pneumoniae) |
|    | 5) Penicillin – Sensitive and Penicillin Producing gonococcus (Neisseria gonorrhoeae [gonococcus])  |
|    | 6) Meningitis (Neisseria meningitidis [meningococcus])  |
| 15 | 7) Typhoid fever, Paratyphoid fever, Bacteremia (Salmonella)  |
|    | 8) Epiglottitis, Meningitis (Haemophilus influenzae)  |
|    | 9) Chancroid (Haemophilus ducreyi)  |
| 20 | 10) Wound infection (animal bite), Abscesses, Bacteremia, Meningitis (Pasteurella multocida)  |
|    | 11) Melioidosis (Pseudomonas pseudomallei)  |
|    | 12) Bacteremia, Endocarditis, Meningitis (Campylobacter fetus)  |
| 25 | 13) Syphilis (Treponema pallidum)   |
|    | 14) Erythema chronica migrans – skin, Stage 2 – neurological, Cardiac, Arthritis (Borrelia burgdorferi [Lyme disease])                          |
|    | 15) Pulmonary lesions, Brain abscess, Lesions of other organs (Nocardia asteroides)   |

## **CEFOTAXIME**

- |    |  |
|----|--|
| 30 | 1) Meningitis (Streptococcus agalactiae [Group B])   |
|    | 2) Pneumonia, Arthritis, Sinusitis, Otitis [Penicillin – Resistant] (Streptococcus pneumoniae [Pneumococcus])                                      |
| 35 | 3) Endocarditis, Meningitis, Other serious infections [Penicillin intermediately- Resistant and Penicillin – Sensitive] (Streptococcus Pneumoniae) |
|    | 4) Endocarditis, Meningitis, Other serious infection [Penicillin G – Resistant] (Streptococcus pneumoniae) + Rifampin or + Vancomycin              |
| 40 | 5) Meningitis (Neisseria meningitidis [meningococcus])   |
|    | 6) Epiglottitis, Meningitis (Haemophilus influenzae)   |

## **CEFTIZOXIME**



- 1) Gas gangrene (*Clostridium perfringens* and other species)
- CEFIXIME
- 1) Penicillin – Sensitive and Penicillinase – Producing gonococcus (*Neisseria gonorrhoeae*)
- 5 CEFTAZIDIME
- 1) Urinary tract infection (*Pseudomonas aeruginosa*)
- 2) Pneumonia, Bacteremia *Pseudomonas aeruginosa* + an Aminoglycoside
- 3) Melioidosis (*Pseudomonas pseudomallei*)
- 10 CEFMENOXIME
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella Catarrhalis*)
- 2) Urinary tract and other infections (*Proteus*, other species)
- 3) Urinary tract and other infections (*Proteus mirabilis*)
- 4) Urinary tract infection (*Klebsiella pneumoniae*)
- 15 5) Pneumonia (*Klebsiella pneumoniae*) ± an Aminoglycoside
- 6) Various nosocomial infections (*Acinetobacter*)
- 7) Yersiniosis, Sepsis (*Yersinia enterocolitica*)
- 8) Variety of nosocomial and opportunistic infections (*Serratia*)
- 20 CEFODIZIME
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
- 2) Urinary tract and other infections (*Proteus*, other species)
- 3) Urinary tract and other infections (*Proteus mirabilis*)
- 4) Urinary tract infection (*Klebsiella pneumoniae*)
- 25 5) Pneumonia (*Klebsiella pneumoniae*) ± an Aminoglycoside
- 6) Various nosocomial infections (*Acinetobacter*)
- 7) Yersiniosis, Sepsis (*Yersinia enterocolitica*)
- 8) Variety of nosocomial and opportunistic infections (*Serratia*)
- 30 CEFDINIR
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
- 2) Urinary tract and other infections (*Proteus*, other species)
- 3) Urinary tract and other infections (*Proteus mirabilis*)
- 4) Urinary tract infection (*Klebsiella pneumoniae*)
- 35 5) Pneumonia (*Klebsiella pneumoniae*) ± an Aminoglycoside
- 6) Various nosocomial infections (*Acinetobacter*)
- 7) Yersiniosis, Sepsis (*Yersinia enterocolitica*)
- 8) Variety of nosocomial and opportunistic infections (*Serratia*)
- 40 CEFETAMET PIVOXIL
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
- 2) Urinary tract and other infections (*Proteus*, other species)
- 3) Urinary tract and other infections (*Proteus mirabilis*)



- 5
- 4) Urinary tract infection (*Klebsiella pneumoniae*)
  - 5) Pneumonia (*Klebsiella pneumoniae*)  $\pm$  an Aminoglycoside
  - 6) Various nosocomial infections (*Acinetobacter*)
  - 7) Yersiniosis, Sepsis (*Yersinia enterocolitica*)
  - 8) Variety of nosocomial and opportunistic infections (*Serratia*)

## CEFTIBUTEN

- 10
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus*, other species)
  - 3) Urinary tract and other infections (*Proteus mirabilis*)
  - 4) Urinary tract infection (*Klebsiella pneumoniae*)
  - 5) Pneumonia (*Klebsiella pneumoniae*)  $\pm$  an Aminoglycoside
  - 6) Various nosocomial infections (*Acinetobacter*)
  - 7) Yersiniosis, Sepsis (*Yersinia enterocolitica*)
  - 15 8) Variety of nosocomial and opportunistic infections (*Serratia*)

## LATAMOXEF (OXACEPHALOSPORIN)

- 20
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus*, other species)
  - 3) Urinary tract and other infections (*Proteus mirabilis*)
  - 4) Urinary tract infection (*Klebsiella pneumoniae*)
  - 5) Pneumonia (*Klebsiella pneumoniae*)  $\pm$  an Aminoglycoside
  - 6) Various nosocomial infections (*Acinetobacter*)
  - 7) Yersiniosis, Sepsis (*Yersinia enterocolitica*)
  - 25 8) Variety of nosocomial and opportunistic infections (*Serratia*)

## CEFPIRAMIDE

- 30
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus*, other species)
  - 3) Urinary tract and other infections (*Proteus mirabilis*)
  - 4) Urinary tract infection (*Klebsiella pneumoniae*)
  - 5) Pneumonia (*Klebsiella pneumoniae*)  $\pm$  an Aminoglycoside
  - 6) Various nosocomial infections (*Acinetobacter*)
  - 7) Yersiniosis, Sepsis (*Yersinia enterocolitica*)
  - 35 8) Variety of nosocomial and opportunistic infections (*Serratia*)

## CEFSULODIN

- 40
- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
  - 2) Urinary tract and other infections (*Proteus*, other species)
  - 3) Urinary tract and other infections (*Proteus mirabilis*)
  - 4) Urinary tract infection (*Klebsiella pneumoniae*)
  - 5) Pneumonia (*Klebsiella pneumoniae*)  $\pm$  an Aminoglycoside



- 6) Various nosocomial infections (*Acinetobacter*)
- 7) Yersiniosis, Sepsis (*Yersinia enterocolitica*)
- 8) Variety of nosocomial and opportunistic infections (*Serratia*)

5

**CEFOPERAZONE**

- 1) Otitis, Sinusitis, Pneumonia (*Moraxella catarrhalis*)
- 2) Urinary tract and other infections (*Proteus*, other species)
- 3) Urinary tract and other infections (*Proteus mirabilis*)
- 4) Urinary tract infection (*Klebsiella pneumoniae*)
- 10 5) Pneumonia (*Klebsiella pneumoniae*) ± an Aminoglycoside
- 6) Various nosocomial infections (*Acinetobacter*)
- 7) Yersiniosis, Sepsis (*Yersinia enterocolitica*)
- 8) Variety of nosocomial and opportunistic infections (*Serratia*)

15

**CEPHALOSPORINS****G4 FOURTH GENERATION****CEFEPIME**

20

- 1) Active against many Enterobacteriaceae that are resistant to other cephalosporins
- 2) Active against *H. influenzae*, *N. gonorrhoeae* and *N. meningitidis*
- 3) High activity for streptococci and Methicillin-Sensitive *Staphylococcus aureus*
- 25 4) Also active against *P. aeruginosa* and *Xanthomonas maltophilia*

25

**H. OTHER  $\beta$  – LACTAM ANTIBIOTICS CARBAPENEMS**

30

**IMIPENEM**

- 1) Gas gangrene (*Clostridium perfringens* and other species)
- 2) Urinary tract and other infections (*Enterobacter* species)
- 3) Urinary tract and other infections (*Proteus*, other species)
- 35 4) Urinary tract infection (*Pseudomonas aeruginosa*)
- 5) Pneumonia, Bacteremia (*Pseudomonas aeruginosa*) + an Aminoglycoside
- 6) Pneumonia (*Klebsiella pneumoniae*)
- 7) Variety of nosocomial and opportunistic infections (*Serratia*)
- 40 8) Various nosocomial infections (*Acinetobacter*)
- 9) Bacteremia, Endocarditis (*Campylobacter fetus*)



- 10) Pulmonary lesions, Brain abscess, Lesions of other organs  
(*Nocardia asteroides*)

**MEROPENEM**

- 1) Active against some Imipenem – Resistant *Pseudomonas aeruginosa*  
2) Urinary tract infection (*Pseudomonas aeruginosa*)

**I. OTHER  $\beta$  – LACTAM ANTIBIOTICS****MONOBAKTAMS****AZTREONAM**

- 1) Urinary tract infection, Other infections, Bacteremia  
(*Escherichia coli*)  
2) Urinary tract and Other infections (*Proteus*, other species)  
3) Urinary tract infection (*Pseudomonas aeruginosa*)  
4) Pneumonia, Bacteremia (*Pseudomonas aeruginosa*) + an  
Aminoglycoside  
5) Pneumonia (*Klebsiella pneumoniae*)  
6) Variety of nosocomial and opportunistic infections  
(*Serratia*)

**J. AMINOGLYCOSIDE****STREPTOMYCIN**

- 1) Urinary tract infection, other infections, Bacteremia.  
(*Escherichia coli*)  $\pm$  Ampicillin  
2) Urinary tract infection and other infections (*Enterobacter*  
species)  
3) Urinary tract infection and other infections (*Proteus*  
*mirabilis*)  
4) Urinary tract infection and other infections (*Proteus*, other  
species)  
5) Urinary tract infection (*Pseudomonas aeruginosa*)  
6) Pneumonia, Bacteremia (*Pseudomonas aeruginosa*) + A  
broad-spectrum Penicillin; + Ciprofloxacin; + Ceftazidime;  
+ Aztreonam; + Imipenem  
7) Urinary tract infection (*Klebsiella pneumoniae*)  
8) Pneumonia (*Klebsiella pneumoniae*) + Mezlocillin or  
Piperacillin  
9) Variety of nosocomial and opportunistic infections  
(*Serratia*) + A broad-spectrum Penicillin  
10) Various nosocomial infections (*Acinetobacter*)  
11) Sepsis (*Yersinia enterocolitica*)



- 5 12) Endocarditis, Infected foreign bodies, Bacteremia  
(*Corynebacterium* species; aerobic and anaerobic  
[diphtheroids]) + Penicillin G
- 13) Bacteremia, Arthritis, Endocarditis, Abscesses  
(*Streptobacillus moniliformis*)
- 14) Pulmonary, Milary, Renal, Meningeal, and other  
tuberculous infections (*Mycobacterium tuberculosis*) +  
Rifampin or Ethambutol
- 10 15) Yaws (*Treponema pertenue*)
- 16) Plague (*Yersinia pestis*) ± Tetracycline
- 17) Tularemia (*Francisella tularensis*)
- 18) Glanders (*Pseudomonas mallei*) + a Tetracycline or +  
Chloramphenicol
- 15 19) Occasionally administrate for tuberculosis (*Mycobacterium  
tuberculosis*)

## GENTAMICIN

- 1) Urinary tract infection, other infections, Bacteremia.  
(*Escherichia coli*) ± Ampicillin
- 20 2) Urinary tract infection and other infections (*Enterobacter  
species*)
- 3) Urinary tract infection and other infections (*Proteus  
mirabilis*)
- 4) Urinary tract infection and other infections (*Proteus*, other  
species)
- 25 5) Urinary tract infection (*Pseudomonas aeruginosa*)
- 6) Pneumonia, Bacteremia (*Pseudomonas aeruginosa*) + A  
broad-spectrum Penicillin; + Ciprofloxacin; + Ceftazidime;  
+ Aztreonam; + Imipenem
- 7) Urinary tract infection (*Klebsiella pneumoniae*)
- 30 8) Pneumonia (*Klebsiella pneumoniae*) + Mezlocillin or  
Piperacillin
- 9) Variety of nosocomial and opportunistic infections  
(*Serratia*) + A broad-spectrum Penicillin
- 10) Various nosocomial infections (*Acinetobacter*)
- 35 11) Sepsis (*Yersinia enterocolitica*)
- 12) Endocarditis, Infected foreign bodies, Bacteremia  
(*Corynebacterium* species; aerobic and anaerobic  
[diphtheroids]) + Penicillin G
- 40 13) Endocarditis or other serious infection [bacteremia]  
(*Enterococcus*) + Penicillin G or Ampicillin; + Vancomycin
- 14) Meningitis, Bacteremia (*Listeria monocytogenes*) +  
Ampicillin or Penicillin G
- 15) Brucellosis (*Brucella*) + Doxycycline



- 16) Tularemia (*Francisella tularensis*)
- 17) Bacteremia, Endocarditis (*Campylobacter fetus*)

## TOBRAMYCIN

- 5           1) Urinary tract infection, other infections, Bacteremia.  
(*Escherichia coli*) ± Ampicillin
- 2) Urinary tract infection and other infections (*Enterobacter*  
species)
- 3) Urinary tract infection and other infections (*Proteus*  
10           *mirabilis*)
- 4) Urinary tract infection and other infections (*Proteus*, other  
species)
- 5) Urinary tract infection (*Pseudomonas aeruginosa*)
- 15           6) Pneumonia, Bacteremia (*Pseudomonas aeruginosa*) + A  
broad-spectrum Penicillin; + Ciprofloxacin; + Ceftazidime;  
+ Aztreonam; + Imipenem
- 7) Urinary tract infection (*Klebsiella pneumoniae*)
- 8) Pneumonia (*Klebsiella pneumoniae*) + Mezlocillin or  
Piperacillin
- 20           9) Variety of nosocomial and opportunistic infections  
(*Serratia*) + A broad-spectrum Penicillin
- 10) Various nosocomial infections (*Acinetobacter*)
- 11) Sepsis (*Yersinia enterocolitica*)
- 25           12) Endocarditis, Infected foreign bodies, Bacteremia  
(*Corynebacterium* species; aerobic and anaerobic  
[diphtheroids]) + Penicillin G

## AMICACIN

- 1) Urinary tract infection, other infections, Bacteremia.  
(*Escherichia coli*) ± Ampicillin
- 30           2) Urinary tract infection and other infections (*Enterobacter*  
species)
- 3) Urinary tract infection and other infections (*Proteus*  
*mirabilis*)
- 4) Urinary tract infection and other infections (*Proteus*, other  
species)
- 35           5) Urinary tract infection (*Pseudomonas aeruginosa*)
- 6) Pneumonia, Bacteremia (*Pseudomonas aeruginosa*) + A  
broad-spectrum Penicillin; + Ciprofloxacin; + Ceftazidime;  
+ Aztreonam; + Imipenem
- 7) Urinary tract infection (*Klebsiella pneumoniae*)
- 40           8) Pneumonia (*Klebsiella pneumoniae*) + Mezlocillin or  
Piperacillin
- 9) Variety of nosocomial and opportunistic infections  
(*Serratia*) + A broad-spectrum Penicillin



- 5
- 10) Various nosocomial infections (*Acinetobacter*)
- 11) Sepsis (*Yersinia enterocolitica*)
- 12) Endocarditis, Infected foreign bodies, Bacteremia (*Corynebacterium* species; aerobic and anaerobic [diphtheroids]) + Penicillin G
- 13) Disseminated disease in AIDS (*Mycobacterium avium* – intracellulare)
- 14) Pulmonary lesions, Brain abscess, Lesions of the other organs
- 10
- NETILMICIN
- 1) Urinary tract infection, other infections, Bacteremia. (*Escherichia coli*) ± Ampicillin
- 2) Urinary tract infection and other infections (*Enterobacter* species)
- 15
- 3) Urinary tract infection and other infections (*Proteus mirabilis*)
- 4) Urinary tract infection and other infections (*Proteus*, other species)
- 20
- 5) Urinary tract infection (*Pseudomonas aeruginosa*)
- 6) Pneumonia, Bacteremia (*Pseudomonas aeruginosa*) + A broad-spectrum Penicillin; + Ciprofloxacin; + Ceftazidime; + Aztreonam; + Imipenem
- 7) Urinary tract infection (*Klebsiella pneumoniae*)
- 25
- 8) Pneumonia (*Klebsiella pneumoniae*) + Mezlocillin or Piperacillin
- 9) Variety of nosocomial and opportunistic infections (*Serratia*) + A broad-spectrum Penicillin
- 10) Various nosocomial infections (*Acinetobacter*)
- 11) Sepsis (*Yersinia enterocolitica*)
- 30
- 12) Endocarditis, Infected foreign bodies, Bacteremia (*Corynebacterium* species; aerobic and anaerobic [diphtheroids]) + Penicillin G
- 13) Effective against certain gentamicin-resistant pathogens, except enterococci
- 35
- KANAMYCIN
- 1) Urinary tract infection, other infections, Bacteremia. (*Escherichia coli*) ± Ampicillin
- 2) Urinary tract infection and other infections (*Enterobacter* species)
- 40
- 3) Urinary tract infection and other infections (*Proteus mirabilis*)
- 4) Urinary tract infection and other infections (*Proteus*, other species)



- |    |                 |  |
|----|-----------------|--|
|    | 5)              | Urinary tract infection ( <i>Pseudomonas aeruginosa</i> )  |
|    | 6)              | Pneumonia, Bacteremia ( <i>Pseudomonas aeruginosa</i> ) + A broad-spectrum Penicillin; + Ciprofloxacin; + Ceftazidime; + Aztreonam; + Imipenem |
| 5  | 7)              | Urinary tract infection ( <i>Klebsiella pneumoniae</i> )   |
|    | 8)              | Pneumonia ( <i>Klebsiella pneumoniae</i> ) + Mezlocillin or Piperacillin   |
|    | 9)              | Variety of nosocomial and opportunistic infections ( <i>Serratia</i> ) + A broad-spectrum Penicillin   |
| 10 | 10)             | Various nosocomial infections ( <i>Acinetobacter</i> )   |
|    | 11)             | Sepsis ( <i>Yersinia enterocolitica</i> )  |
|    | 12)             | Endocarditis, Infected foreign bodies, Bacteremia ( <i>Corynebacterium</i> species; aerobic and anaerobic [diphtheroids]) + Penicillin G       |
| 15 | 13)             | Orally for the prophylactic use as adjunctive therapy in cases of hepatic coma   |
|    | <b>NEOMYCIN</b> |  |
|    | 1)              | Urinary tract infection, other infections, Bacteremia. ( <i>Escherichia coli</i> ) ± Ampicillin  |
| 20 | 2)              | Urinary tract infection and other infections ( <i>Enterobacter</i> species)  |
|    | 3)              | Urinary tract infection and other infections ( <i>Proteus mirabilis</i> )  |
| 25 | 4)              | Urinary tract infection and other infections ( <i>Proteus</i> , other species)   |
|    | 5)              | Urinary tract infection ( <i>Pseudomonas aeruginosa</i> )  |
|    | 6)              | Pneumonia, Bacteremia ( <i>Pseudomonas aeruginosa</i> ) + A broad-spectrum Penicillin; + Ciprofloxacin; + Ceftazidime; + Aztreonam; + Imipenem |
| 30 | 7)              | Urinary tract infection ( <i>Klebsiella pneumoniae</i> )   |
|    | 8)              | Pneumonia ( <i>Klebsiella pneumoniae</i> ) + Mezlocillin or Piperacillin   |
|    | 9)              | Variety of nosocomial and opportunistic infections ( <i>Serratia</i> ) + A broad-spectrum Penicillin   |
| 35 | 10)             | Various nosocomial infections ( <i>Acinetobacter</i> )   |
|    | 11)             | Sepsis ( <i>Yersinia enterocolitica</i> )  |
|    | 12)             | Endocarditis, Infected foreign bodies, Bacteremia ( <i>Corynebacterium</i> species; aerobic and anaerobic [diphtheroids]) + Penicillin G       |
| 40 | 13)             | For bladder irrigation + Polymyxin B   |
|    | 14)             | Variety of infections of the skin and mucous membranes caused by microorganisms susceptible to the drug. These                                 |



include infections associated with burns, wounds, ulcers, and infection dermatoses.

# **K. TETRACYCLINE**

## TETRACYCLINE

- 5           1) Sinusitis (*Moraxella catarrhalis*)
- 2) Plague (*Yersinia pestis*) ± Streptomycin
- 3) Glanders (*Pseudomonas mallei*) + Streptomycin
- 4) Stage 2 - Neurological, cardiac, arthritis (*Borrelia burgdorferi* [Lyme disease])

## 10           CHLORTETRACYCLINE

## OXYTETRACYCLINE

## DOXYCYCLINE

- 1) Erysipeloid (*Erysipelothrix rhusiopathiae*)
- 2) Gas gangrene (*Clostridium perfringens* & other species)
- 15       3) Tetanus (*Clostridium tetani*)
- 4) Urinary tract infection (*Escherichia coli*)
- 5) Brucellosis (*Brucella*) + Gentamicin or Rifampin
- 6) Chancroid (*Haemophilus ducreyi*)
- 7) Plague (*Yersinia pestis*)
- 20       8) Wound infection-animal bite (*Pasteurella multocida*)
- 9) Cholera (*Vibrio cholerae*)
- 10) Lung abscess, empyema (*Fusobacterium nucleatum*)
- 11) Arthritis (*Streptobacillus moniliformis*)
- 12) Syphilis (*Treponema pallidum*)
- 25       13) Yaws (*Treponema pertenue*)
- 14) Erythema chronica migrans-skin (*Borrelia burgdorferi*[Lyme disease])
- 15) Relapsing fever (*Borrelia recurrentis*)
- 16) Weil's disease and meningitis (*Leptospira*)
- 30       17) Cervicofacial, abdominal, thoracic, and other lesions (*Actinomyces israelii*)
- 18) Non-specific urethritis (*Ureaplasma urealyticum*)
- 19) "Atypical pneumonia" (*Mycoplasma pneumoniae*)
- 35       20) Typhus fever, Murine typhus, Brill's disease, Rocky Mountain spotted fever, Q fever, and Rickettsialpox (*Rickettsia*)
- 21) Psittacosis (*Chlamydia psittaci*)
- 22) Lymphogranuloma venereum, Trachoma, Inclusion conjunctivitis (blennorrhoea), Non-specific urethritis, Cervicitis (*Chlamydia trachomatis*)
- 40       23) Pneumonia (*Chlamydia pneumoniae*)



MINOCYCLINE

DEMECLOCYCLINE

METHACYCLINE

5 **L. CHLORAMPHENICOL**

CHLORAMPHENICOL

- 1) Meningitis (*Streptococcus agalactiae* [Group B])
- 2) Bacteremia, Endocarditis, Brain and other abscesses, and Sinusitis (*Streptococcus* [anaerobic species])
- 10 3) Pneumonia, Arthritis, Sinusitis, Otitis, Endocarditis, Meningitis, Other serious infections (*Streptococcus pneumoniae* [pneumococcus]).
- 4) Meningitis (*Neisseria meningitidis* [meningococcus])
- 5) "Malignant pustule", Pneumonia (*Bacillus anthracis*)
- 15 6) Bacteremia (*Listeria monocytogenes*)
- 7) Erysipeloid (*Erysipelothrix rhusiopathiae*)
- 8) Gas gangrene (*Clostridium perfringens* and other species)
- 9) Typhoid fever, Paratyphoid fever, Bacteremia (*Salmonella*)
- 20 10) Epiglottitis, Meningitis (*Haemophilus influenza*)
- 11) Brucellosis (*Brucella*)
- 12) Plague (*Yersinia pestis*)
- 13) Sepsis (*Yersinia enterocolitica*)
- 14) Tularemia (*Francisella tularensis*)
- 25 15) Cholera (*Vibrio cholerae*)
- 16) Glanders (*Pseudomonas mallei*) + Streptomycin
- 17) Melioidosis (*Pseudomonas pseudomallei*)
- 18) Meningitis (*Campylobacter fetus*)
- 30 19) Ulcerative pharyngitis, Lung abscess and Empyema, Genital infections, Gingivitis (*Fusobacterium nucleatum*)
- 20) Bacteremia, Arthritis, Endocarditis, Abscesses (*Streptobacillus moniliformis*)
- 21) Typhus fever, Murine typhus, Brill's disease, Rocky mountain spotted fever, Q fever, Rickettsialpox (*Rickettsia*)
- 35 22) Psittacosis [ornithosis] (*Chlamydia psittaci*)

THIAMPHENICOL

AZIDAMPHENICOL

40 **M. ERYTHROMYCIN AND OTHERS**

MACROLIDES:



## ERYTHROMYCIN

- 1) Abscesses, Bacteremia, Endocarditis, Pneumonia  
Osteomyelitis, Cellulitis and other Staph. aureus  
infections [Methicillin – Sensitive] (Staphylococcus  
aureus)
- 2) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis,  
Erysipelas, Pneumonia, Bacteremia, toxic shock – like  
syndrome, and other systemic infections (Streptococcus  
pyogenes [Group A])
- 3) Bacteremia, Endocarditis, Brain and other abscesses,  
Sinusitis (Streptococcus [anaerobic species])
- 4) Penicillin – Sensitive gonococcus (Neisseria gonorrhoeae)
- 5) "Malignant pustule", Pneumonia (Bacillus anthracis)
- 6) Pharyngitis, Laryngotracheitis, Pneumonia, and other local  
lesions, Carrier state (Corynebacterium diphtheriae)
- 7) Bacteremia (Listeria monocytogenes)
- 8) Chancroid (Haemophilus ducreyi)
- 9) Enteritis (Campylobacter jejuni)
- 10) Ulcerative pharyngitis, Lung abscess, Empyema, Genital  
infections, Gingivitis (Fusobacterium nucleatum)
- 11) Bacteremia, Arthritis, Endocarditis, Abscesses  
(Streptobacillus moniliformis)
- 12) Legionnaires' disease (Legionella pneumophila) ± rifampin
- 13) Relapsing fever (Borrelia recurrentis)
- 14) Cervicofacial, Abdominal, Thoracic and other lesions  
(Actinomyces israelii).
- 15) Non-specific Urethritis (Ureaplasma Urealyticum)
- 16) "Atypical pneumonia" (Mycoplasma pneumoniae)
- 17) Lymphogranuloma venereum, Trachoma, Inclusion  
conjunctivitis [blennorrhoea], Non-specific urethritis,  
Cervicitis (Chlamydia trachomatis)
- 18) Pneumonia (Chlamydia pneumoniae)
- 19) Erysipeloid (Erysipelothrix rhusiopathiae)
- 20) Bordetella pertussis disease and for post-exposure  
prophylaxis of all household member and other close  
contacts.
- 21) Tetanus in patients who are allergic to penicillin  
(Clostridium tetani)

## CLARITHROMYCIN

- 1) Legionnaires' disease (Legionella pneumophila)
- 2) "Atypical pneumonia" (Mycoplasma pneumoniae)
- 3) Pneumonia (Chlamydia pneumoniae)



- 4) Enteritis (*Campylobacter jejuni*)
- 5) Disseminated disease in AIDS (*Mycobacterium avium* — intracellulare) + Ethambutol; ± Clofazimine; ± Ciprofloxacin
- 6) Erythema chronica migrans – skin (*Borrelia burgdorferi* [Lyme disease])
- 7) Modest activity against *H. influenzae* and *N. gonorrhoeae*
- 8) Good activity against *M. catarrhalis*
- 9) Enhanced activity against some protozoa (e.g., *Toxoplasma gondii*, *Cryptosporidium* and *Plasmodium* spp.
- 10) Regimens for the treatment of peptic ulcers related to *H. pylori* infection
- 11) Lepromatous leprosy (*Mycobacterium leprae*) + minocycline

**AZITHROMYCIN**

- 1) Otitis media, Sinusitis, Pneumonia (*Haemophilus influenzae*)
- 2) Enteritis (*Campylobacter jejuni*)
- 3) Legionnaires' disease (*Legionella pneumophila*)
- 4) Erythema chronica migrans – skin (*Borrelia burgdorferi* [Lyme disease])
- 5) "Atypical pneumonia" (*Mycoplasma pneumoniae*)
- 6) Lymphogranuloma venereum, Trachoma, Inclusion conjunctivitis [blennorrhoea], Non-specific urethritis, Cervicitis (*Chlamydia trachomatis*)
- 7) Pneumonia (*Chlamydia pneumoniae*)
- 8) Less active against *Streptococcus* spp. And Enterococci
- 9) Active against *M. catarrhals*, *Pasteurella multocida*, *Fusobacterium* spp., *N. gonorrhoeae*
- 10) Enhanced activity against *Mycobacterium avium-intracellulare*, as well as against protozoa (e.g. *Toxoplasma gondii*, *Cryptosporidium* and *Plasmodium* spp.
- 11) Toxoplasmosis encephalitis and diarrhoea due to *Cryptosporidium*

**ROXITHROMYCIN****N. LINCOMYCIN****CLINDAMYCIN**

- 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis and other *Staphylococcus aureus*



infections [Methicillin – Sensitive] (*Staphylococcus aureus*).

- 2) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome, and other systemic infections (*Streptococcus pyogenes* [Group A])
- 3) Bacteremia, Endocarditis, Brain and other abscesses, Sinusitis (*Streptococcus* [anaerobic species])
- 4) Pneumonia, Arthritis, Sinusitis, Otitis [Penicillin – Sensitive and Penicillin – Resistant] (*Streptococcus pneumoniae*)
- 5) Pharyngitis, Laryngotracheitis, Pneumonia, Other local lesions (*Corynebacterium diphtheriae*)
- 6) Gas gangrene (*Clostridium perfringens* and other species)
- 7) Tetanus (*Clostridium tetani*)
- 8) Enteritis (*Campylobacter jejuni*)
- 9) Ulcerative pharyngitis, Lung abscess, Empyema, Genital infections, Gingivitis
- 10) Pneumonia in impaired host [Mild or moderate disease and moderately severe or severe disease] (*Pneumocystis carinii*) + Primaquin
- 11) Treatment of infections with anaerobes, especially those due to *B. fragilis*
- 12) Intra-abdominal or pelvic abscesses and peritonitis + an Aminoglycoside or + Penicillin or + Cephalothin
- 13) Topically or orally for acne vulgaris and for bacterial vaginosis

#### SPECTINOMYCIN

- 1) Penicillin – Sensitive and Penicillinase-Producing gonococcus (*Neisseria gonorrhoeae*)
- 2) In pregnancy when patients are intolerant to  $\beta$ -Lactams and when quinolones are contraindicated
- 3) Recommended as an alternative regimen in patients who are intolerant or allergic to  $\beta$ -Lactam antibiotics and quinolones

#### POLYMYXIN B (Polymyxin B Sulfate)

- 1) Available for ophthalmic, otic and topical use in combination with a variety of other compounds.
- 2) Infections of the skin, mucous membranes, eye, and ear due to polymyxin B – sensitive microorganisms
- 3) External otitis, frequently due to *Pseudomonas*
- 4) Infection of corneal ulcers (*Pseudomonas aeruginosa*)



5) Pneumonia (Pseudomonas)

COLISTIN (Colisten Sulfate)

- 1) Diarrhoea caused by bacteria susceptible to the drug in infants and children

RAMOPLANIN (glycopeptide)

- 1) Treatment of acne and skin infections, and to reduce nasal carriage of staphylococci  
Active against Bacteroides spp.

TEICOPLANIN (glycopeptide)

- 1) Osteomyelitis, Endocarditis caused by Methicillin – Resistant and Methicillin – Susceptible Staphylococci, Streptococci and Enterococci
- 2) Bacteremia, Endocarditis [methicillin – susceptible] (Staphylococcus aureus) + an Aminoglycoside [gentamycin]
- 3) Enterococcal endocarditis + Gentamicin
- 4) Endocarditis + Vancomycin

BACITRACIN

- 1) Infected eczema, Infected dermal ulcers
- 2) Suppurative conjunctivitis and infected corneal ulcer when they are caused by susceptible bacteria
- 3) Eradication of nasal carriage of Staphylococci
- 4) Antibiotic – associated diarrhoea (Clostridium difficile)

RP 59500

- 1) Is a good inducer of the methylase enzyme that mediates MLS resistance
- 2) Are synergistic and therefore, erythromycin-resistant organisms frequently are susceptible to RP 59500 in vitro

GLYCYLCYCLINES (Tetracycline Antibiotic derivatives)

- 1) They inhibit some tetracycline-resistant organisms
- 2) Also appear to be active against multiply drug-resistant strains of Staphylococci, pneumococci and vancomycin-resistant enterococci

GLYCOPEPTIDE AND OTHER:

VANCOMYCIN

- 1) Abscesses, Bacteremia, Endocarditis, Pneumonia, Osteomyelitis, Cellulitis and other Staphylococcus aureus



infections [Methicillin – Sensitive and Methicillin Resistant]  
(Staphylococcus aureus)

- 2) Pharyngitis, Scarlet fever, Otitis media, Sinusitis, Cellulitis, Erysipelas, Pneumonia, Bacteremia, Toxic shock – like syndrome, and other systemic infections (Streptococcus pyogenes [Group A])
- 3) Endocarditis, Bacteremia (Streptococcus [Viridans Group])
- 4) Bacteremia, Endocarditis (Streptococcus agalactiae [Group B])
- 5) Pneumonia, Arthritis, Sinusitis, Otitis [Penicillin – Resistant] (Streptococcus pneumoniae).
- 6) Endocarditis, Meningitis, Other serious infections [Penicillin – intermediately Resistant] (Streptococcus pneumoniae) + Rifampin
- 7) Endocarditis, Meningitis, Other serious infections [Penicillin G – Resistant] (Streptococcus pneumoniae) + Rifampin or + Cefotaxime
- 8) Endocarditis or other serious infection [bacteremia] (Enterococcus) + Gentamycin
- 9) Urinary tract infection (Enterococcus)
- 10) Endocarditis, Infected foreign bodies, Bacteremia (Corynebacterium species, aerobic and anaerobic [diphtheroids])
- 11) Tetanus (Clostridium tetani)
- 12) Antibiotic – associated colitis (Clostridium difficile)
- 13) Meningitis (Flavobacterium meningosepticum)
- 14) Pseudomembranous colitis
- 15) Staphylococcal infections in patients who are allergic to penicillins and cephalosporins

**O. Drugs Used in the Treatment of Tuberculosis, Mycobacterium avium Complex, and Leprosy**

AMIKACIN  
AMINOSALICYCLIC ACID  
AZITHROMYCIN  
CAPREOMYCIN  
CEFOXITIN  
CIPOFLOXACIN  
CLARITHROMYCIN  
CLOFAZIMINE  
DAPSONE  
DOXYCYCLINE



45

5 ETHAMBUTOL  
 ETHIONAMIDE  
 IMIPENEM  
 ISONIAZID  
 KANAMYCIN  
 MINOCYCLINE  
 OFLOXACIN  
 OFLOXACIN  
 PYRAZINAMIDE  
 10 RIAMPIN  
 RIFABUTIN  
 RIFAMPIN  
 STREPTOMYCIN  
 SULFONAMIDE  
 15 TRIMETHOPRIM-SULFAMETHOXAZOLE,

**P. OTHER TREATMENTS**

RIFAMPIN

- 20 1) Abscesses, Bacteremia, Endocarditis, Pneumonia,  
 Osteomyelitis, Cellulitis, Other [Methicillin-Sensitive  
 Methicillin-Resistant] (Staphylococcus aureus) +  
 Ciprofloxacin or [+ Trimethoprim-sulfamethoxazole when  
 methicillin-resistant]  
 25 2) Endocarditis, Meningitis, Other serious infection  
 [Penicillin-Intermediately resistant] (Streptococcus  
 pneumoniae (pneumococcus)) + Vancomycin  
 3) Endocarditis, Meningitis, Other serious infection [Penicillin  
 G-resistant] (Streptococcus pneumoniae  
 (pneumococcus)) + Cefotaxime or + Vancomycin  
 30 4) Carrier state (post-treatment) (Neisseria meningitidis  
 (meningococcus))  
 5) Pharyngitis, Laryngotracheitis, Pneumonia, Other local  
 lesions (Corynebacterium diphtheriae)  
 35 6) Endocarditis, Infected foreign bodies, Bacteremia  
 (Corynebacterium species, aerobic and anaerobic  
 (diphtheroids)) + Penicillin G  
 7) Brucellosis (Brucella) + Doxycycline or + Trimethoprim  
 8) Meningitis (Flavobacterium meningosepticum)  
 40 9) Legionnaires' disease (Legionella pneumophila) +  
 Erythromycin

**Q. ANTI-FUNGAL AGENTS**

AMPHOTERICIN B  
 AMPHOTERICIN B



5           AMPHOTERICIN B  
          AMPHOTERICIN B  
          AMPHOTERICIN B  
          AMPHOTERICIN B  
          AMPHOTERICIN B

10           AMPHOTERICIN B,  
          BUTOCONAZOLE  
          CICLOPIROX  
          CICLOPIROX  
          CLOTRIMAZOLE  
          CLOTRIMAZOLE  
          CUTANEOUS  
          ECONAZOLE  
          ECONAZOLE  
15           EXTRACUTANEOUS  
          FLUCONAZOLE  
          FLUCONAZOLE  
          FLUCONAZOLE

20           FLUCONAZOLE  
          FLUCONAZOLE,  
          FLUCYTOSINE  
          GRISEOFULVIN  
          HALOPROGIN  
          INTRATHECAL  
25           IODIDE, ITRACONAZOLE

          ITRACONAZOLE  
          ITRACONAZOLE

30           ITRACONAZOLE,  
          ITRACONAZOLE,  
          ITRACONAZOLE,  
          IV MICONAZOLE

35           KETOCONAZOLE  
          KETO-CONAZOLE  
          KETO-CONAZOLE  
          KETO-CONAZOLE  
          KETOCONAZOLE,  
          MICONAZOLE  
          MICONAZOLE



MICONAZOLE NYSTATIN  
 NAFTIFINE  
 NYSTATIN  
 NYSTATIN

5 SPOROTRICHOSIS

SYSTEMIC  
 TERBINAFINE  
 TERBINAFINE  
 TERCONAZOLE  
 10 TIOCONAZOLE  
 TOPICAL CLOTRIMAZOLE  
 UNDECYLENATE

**R. OTHER TREATMENTS**

15 POLIEN ANTIBIOTICS  
 AMPHOTERICIN B

- 1) Deep infection (Candida species) ± Flucytosine
- 2) Disseminated (non-meningeal), Meningitis (Coccidioides immitis)
- 20 3) Chronic Pulmonary disease, Disseminated (Histoplasma capsulatum)
- 4) All the Blastomyces brasiliensis infections
- 5) All the paracoccidioides brasiliensis infections followed up by a sulfonamide
- 25 6) Extracutaneous (Sporothrix schenckii)
- 7) Invasive (Aspergillus species)
- 8) All the infections of the mucormycosis Agents
- 9) Pulmonary (Cryptococcus neoformans)
- 10) Meningitis (Cryptococcus neoformans) ± Flucytosine

30 NYSTATIN

- 1) Cutaneous or vaginal thrush, oral thrush (Candida species)

**FLUCYTOSINE**

- 1) Deep infections (Candida species) + Amphotericin B
- 35 2) Meningitis (Cryptococcus neoformans) + Amphotericin B

**POVIDONE IODINE**

Povidone-iodine is an iodophore which is used as a disinfectant and antiseptic mainly for the treatment of contaminated wounds



and pre-operative preparation of the skin and mucous membranes as well as for the disinfection of equipment.

## **S. IMIDAZOLES AND TRIAZOLES**

5

### **KETOCONAZOLE**

- 1) Cutaneous or vaginal thrush, Oral thrush, (*Candida* species)
- 2) Chronic pulmonary disease (*Histoplasma capsulatum*)
- 3) All *Blastomyces dermatitidis* infections.
- 10 4) All *Paracoccidioides brasiliensis* infections

### **ITRACONAZOLE**

- 1) Cutaneous or vaginal thrush, Oral thrush (*Candida* species)
- 15 2) Disseminated (non-meningeal), Meningitis (*Coccidioides immitis*)
- 3) Disseminated (*Histoplasma capsulatum*)
- 4) Cutaneous, Extracutaneous (*Sporothrix schenckii*)
- 5) Invasive (*Aspergillus* species)
- 6) Chronic pulmonary disease (*Histoplasma capsulatum*)
- 20 7) All *paracoccidioides brasiliensis* infections
- 8) All *Blastomyces dermatitidis* infections

### **FLUXONAZOLE**

- 1) Cutaneous or vaginal thrush, Oral thrush, Deep infection (*Candida* Species)
- 25 2) Disseminated (non-meningeal), Meningitis (*Coccidioides immitis*)
- 3) Chronic pulmonary disease (*Histoplasma capsulatum*)
- 4) Meningitis (*Cryptococcus neoformans*)

30

### **CLOTRIMAZOLE**

- 1) Oral thrush (*Candida* Species)

### **GRISEOFULVIN**

- 1) Mycotic disease of the skin, hair and nails due to *Microsporum*, *Trichophyton* or *Epidermophyton*
- 35 2) *Tinea capitis* (*M. canis*, *M. audouinii*; *T. schoenleinii* and *T. verrucosum*)
- 3) "Ringworm" of the glabrous skin, *Tinea cruris* and *tinea corporis* (*M. canis*, *T. rubrum*, *T. verrucosum* and *E. floccosum*)
- 40 4) *Tinea* of the hands (*T. rubrum*, *T. mentagraphytes*)
- 5) *Tinea* of the beard (*Trichopyton* species)



- 6) "Athlete's foot" or epidermophytosis involving the skin and nails (T. mentagrophytes and the hyperkeratotic type to T. rubrum).

5 **T. TOPICAL ANTI-FUNGAL AGENTS**  
Imidazoles and Triazoles for Topical Use

CLOTRIMAZOLE

- 1) Dermatophyte infections, Cutaneous candidiasis,  
10 Vulvovaginal candidiasis

ECONAZOLE

MICONAZOLE

- 1) Tinea pedis, Tinea cruris, Tinea versicolor  
2) Vulvovaginal candidiasis  
15 3) Some vaginal infections caused by Candida glabrata

TERCONAZOLE

- 1) Vaginal Candidiasis

BUTOCONAZOLE

- 1) Vaginal Candidiasis

20 TIOCONAZOLE

- 1) Candida Vulvovaginitis

OXICONAZOLE

- 1) Infections caused by the common pathogenic  
25 dermatophytes

SULCONAZOLE

- 1) Infections caused by the common pathogenic  
dermatophytes

30 **U. OTHER ANTI-FUNGAL AGENTS FOR TOPICAL USE**

CICLOPIROX OLAMINE

- 1) Cutaneous candidiasis, Tinea corporis, Tinea cruris, Tinea  
pedis, Tinea versicolor  
2) Dermatophytes and candidal infections

HALOPROGIN

- 1) Tinea pedis, Tinea cruris, Tinea corporis, Tinea manuum  
35 and Tinea versicolor

TOLNAFTATE

- 1) Tinea pedis

NAFTIFINE

- 1) Treatment of Tinea cruris and Tinea corporis  
40 2) Cutaneous candidiasis and Tinea versicolor

TERBINAFINE

- 1) Tinea corporis, Tinea cruris, Tinea pedis



- 2) Cutaneous candidiasis and Tinea versicolor
- 3) Treatment of ringworm and in some cases of onychomycosis

5 **V. MISCELLANEOUS ANTI-FUNGAL AGENTS**

UNDECYLENIC ACID

- 1) Treatment of various dermatomycoses, especially Tinea pedis
- 2) Treatment of diaper rash, Tinea cruris and other minor dermatologic conditions

10 **BENZOIC ACID AND SALICYLIC ACID**

- 1) Treatment of Tinea pedis and sometimes used to treat Tinea capitis

**PROPIONIC ACID AND CAPRYLIC ACID**

- 1) Treatment of the dermatomycoses

15 **POTASSIUM IODIDE**

- 1) Cutaneous (*Sporothrix schenckii*)

**W. ANTI-FUNGAL AGENTS FOR OPHTHALMIC USE**

20 **NATAMYCIN**

Fungal blepharitis, conjunctivitis, keratitis

**IMIDAZOLES CLOTRIMAZOLE**

Fungal keratitis

**ECONAZOLE**

25 Fungal keratitis

**FLUCONAZOLE**

Fungal keratitis

**KETOCONAZOLE**

Fungal keratitis

30 **MICONAZOLE**

Fungal keratitis, endophthalmitis

**PYRIMIDINES**

**FLUCYTOSINE**

Fungal keratitis

35 **POLYENES**

**AMPHOTERICIN B**

Fungal keratitis, endophthalmitis



**X. ANTI-VIRAL AGENTS****ANTI-HERPESVIRUS AGENTS:****ACYCLOVIR**

- 1) Genital disease, Keratoconjunctivitis, Encephalitis, Neonatal HSV, Mucocutaneous HSV in immuno-compromised host (Herpes simplex virus)
- 2) Herpes zoster or varicella in immuno-compromised host, pregnancy, Varicella or herpes zoster in normal host (Varicella zoster virus)

**VALACYCLOVIR**

- 1) Genital herpes or localised herpes zoster

**FAMCICLOVIR**

- 1) Varicella or herpes zoster in normal host (Varicella zoster virus)

**PENCICLOVIR**

- 1) It is inhibitory for hepatitis B virus

**FOSCARNET**

- 1) Retinitis in patients with AIDS (Cytomegalovirus)
- 2) Mucocutaneous HSV in immuno-compromised host (Herpes simplex virus)
- 3) Herpes zoster or varicella in immuno-compromised host, pregnancy (Varicella zoster virus)

**GANCICLOVIR**

- 1) Retinitis in patients with AIDS (Cytomegalovirus)

**IDOXURIDINE**

- 1) Keratoconjunctivitis (Herpes simplex virus)

**SORIVUDINE**

- 1) Herpes zoster in HIV – infected adults

**TRIFLURIDINE**

- 1) Keratoconjunctivitis (Herpes simplex virus)

**VIDARABINE**

- 1) Encephalitis, neonatal herpes (Herpes simplex virus)
- 2) Zoster or varicella in immuno-compromised patients

**Y. ANTI-RETROVIRAL AGENTS****ZIDOVUDINE**

- 1) AIDS, HIV antibody positive and CD4 count less than 500/mm<sup>3</sup> (Human Immuno-deficiency virus)

**DIDANOSINE**

- 1) Advanced HIV infections in adults and children over 6 months



## STAVUDINE

- 1) AIDS, HIV antibody positive and CD4 count less than 400/mm<sup>3</sup> (Human immuno-deficiency virus)

## ZALCITABINE

- 1) AIDS
- 2) HIV infection and CD4 count less than 300/mm<sup>3</sup>

**Z. OTHER ANTI-VIRAL AGENTS**

## AMANTADINE

- 1) Influenza (Influenza A)

## RIMANTADINE

- 1) Influenza (Influenza A)

## INTERFERONS ALFA

- 1) Genital papilloma (Human papilloma virus)

## RIBAVIRIN

- 1) Pneumonia and bronchiolitis of infancy (Respiratory syncytial virus)

**AA. NEWER AGENTS UNDER CLINICAL DEVELOPMENT**

## LAMIVUDINE

## PROTEASE INHIBITORS

## ACYCLIC NUCLEOSIDE PHOSPHONATES

**AB. ANTI-VIRAL AGENTS FOR OPHTHALMIC USE**

## IDOXURIDINE (HERPLEX)

- 1) Herpes simplex keratitis

## TRIFLURIDINE (VIOPTIC)

- 1) Herpes simplex keratitis

## VIDARABINE (VIRA-A)

- 1) Herpes simplex keratitis
- 2) Herpes simplex conjunctivitis

## ACYCLOVIR (ZOVIRAX)

- 1) Herpes zoster ophthalmicus
- 2) Herpes simplex keratitis

## FOSCARNET (FOSCAVIR)

- 1) Cytomegalovirus retinitis

## GANCICLOVIR (CYTOVENE)

- 1) Cytomegalovirus retinitis

**AC. Topical Antibacterial Agents Commercially Available for Ophthalmic Use**

## BACITRACIN ZINC (AK-TRACIN)



1) Conjunctivitis, blepharitis

CHLORAMPHENICOL (AK-CHLOR, CHLOROMYCETIN, CHLOROPTIC,  
OCU-CHLOR)

1) Conjunctivitis, keratitis

CHLORTETRACYCLINE HYDROCHLORIDE  
(AUREOMYCIN)

1) Conjunctivitis, blepharitis

CIPROFLOXACIN HYDROCHLORIDE (CILOXAN)

1) Conjunctivitis, keratitis

ERYTHROMYCIN (AK-MYCIN, ILOTYCIN)

1) Blepharitis, conjunctivitis

GENTAMICIN SULFATE (GARAMYCIN, GENOTIC, GENT-AK,  
GENTACIDIN)

1) Conjunctivitis, blepharitis, keratitis

NORFLOXACIN (CHIBROXIN)

1) Conjunctivitis

SULFACETAMIDE SODIUM

(AK-SULF, BLEPH-10, CETAMIDE, SULF-10, ISOPTO CETAMIDE,  
OPHTHACET, SULAMYD SODIUM)

1) Conjunctivitis, blepharitis, keratitis

SULFISOXAZOLE DIOLAMINE (GANTRISIN)

1) Conjunctivitis, blepharitis, keratitis

POLYMYXIN B COMBINATIONS

1) Conjunctivitis, blepharitis, keratitis

TETRACYCLINE HYDROCHLORIDE (ACHROMYCIN)

1) Conjunctivitis, blepharitis

TOBRAMYCIN SULFATE (TOBREX)

1) Conjunctivitis, blepharitis, keratitis



## PRELIMINARY HYPOTHESES OF MECHANISM OF OPERATION

The mechanism by which the enhancement of action of anti-infective drugs is achieved by the present invention, is currently under investigation. Some observations in this regard have been recorded above. In addition it is recorded that preliminary observations point to some additional possible explanations. The applicant again does not wish to be bound to any of the tentative explanations it may put forward at this time. It is recorded, however, that it would appear that the long chain fatty acids used in the formulation of the preparation according to the invention, or at least some of these components, form, during the manufacturing process of the medicinal formulation, very small spherical bodies, hereinafter referred to as "nanolipid vesicles". These nanolipid vesicles have dynamic characteristics in respect of the encapsulation and subsequent delivery of compounds at predicted areas in cells and organisms where the optimal utilisation of these compounds occur with resultant maximised modes of actions.

The present model for the understanding of the invention is that the dynamic delivery characteristics of the nanolipid vesicles are utilised efficiently to transport compounds to locations where maintenance of optimal concentrations in the organisms is beneficial in combating specific infective diseases.

Infectious diseases, especially those which are known to develop resistance to compounds are known to be difficult to treat due to insufficient penetration of the compound into the causative microorganisms. These, or at least some of these appear to be particularly suited for the benefits of the present invention.

The composition of the invention has thus been found to have beneficial drug delivery effects when exposed to cells and causative organisms harboured by such cells.

These beneficial effects are believed to be attributable to the dynamic characteristics of the nanolipid vesicles. The current hypothesis is that these characteristics include:

### **1. The structural characteristics of the formulation of the preparation:**



Nitrous oxide and the unsaturated long chain fatty acids forming part of the administration medium are formulated by being mixed with designated anti-infective agents or compounds to form the nanolipid vesicles containing the compound or anti-infective agent. Two important observations have been made in this regard:

- a) It was found that when the unsaturated long chain fatty acids used are 20 carbons or more, the nanolipid vesicles form spherical structures with sub-compartments similar to those seen in a sponge.

These structures are stable and it is our belief that antibodies or other ligands would fit ideally in these sub-compartments so that the nanolipid vesicles bind to specific epitopes or receptors at the target cell surface.

- b) When unsaturated long chain fatty acids of 16 to 20 carbons are used, the form of the nanolipid vesicles is spherical with a dynamic field of moving autofluorescent particles surrounding the vesicles.

When nitrous oxide is omitted from the process the moving particles surrounding the nanolipid vesicles move erratically and asymmetrical movements are then detected.

It is believed that nitrous oxide is essential in stabilising the moving autofluorescent particles surrounding the nanolipid- vesicles, which is an essential characteristic to efficient compound delivery.

## **2. Stability:**

The nanolipid vesicles appear to remain structurally intact after 24 months at room temperature. Any encapsulated active compounds remain encapsulated during this time. This stability feature is believed to be of substantial significance and one of the contributing factors for the enhancement observed.

## **3. Absence of cytotoxicity:**

The nanolipid vesicles have no apparent cytotoxicity. When applied to cells in culture, at applicable concentrations they appear rather to have a beneficial effect on normal cell growth.



#### 4. Mechanism of action:

##### 4.1 Loading efficiency:

5 The high loading efficiency of nanolipid vesicles has been demonstrated by achieving a high degree of encapsulation of a wide range of active drugs.

##### 4.2 Transport:

10 The nanolipid vesicles behave as a transport mechanism to carry molecules such as active compounds.

##### 4.3 Release:

15 It has been shown that the nanolipid vesicles have very high delivery efficiencies. The high delivery efficiency relates to tissue penetration, cell adsorption, internalisation of nanolipid vesicles by cells, parasites and bacteria, intra-cellular stability, and subsequent sub-cellular organelle delivery.

20 The result of high delivery efficiency is the release of active compounds not only at membrane sites, but also at intracellular sites including the nuclei of viable cells or microorganisms. The result is an enhanced efficacy of said active compound. The nanolipid vesicles and active compound appear to act synergistically in attaining enhanced efficacy.

#### 5. Elasticity:

30 Confocal laser scanning microscopy (CLSM) shows that the conformation of nanolipid vesicles can be changed while in movement.

35 When the vesicles move through membranes, the conformation changes so that the intracellular nanolipid vesicles may have other morphological characteristics.

40 While moving through membranes the nanolipid vesicles 'feed' the membranes with unsaturated long chain fatty acids which in its turn will have a positive effect on membrane bound processes. This



process has a positive effect on the metabolism of the cell and thus the survival of the cells.

5    **6.    Dynamic inter-lipid vesicle relationships:**

It has been shown that vesicle inter-lipid relationships do exist. The lipid vesicles can interchange the compounds they respectively carry.

10

They can also combine to resize themselves continuously without detriment to their stability. The inter-lipid relationship is also revealed when moving through the cellular membrane.

15

These interactive membrane characteristics make the movement of the vesicles through the cells optimal.

20

Although inter-relationships of the dynamic nanolipid vesicles are continuously present, it has also been shown that the particles are stable in blood and body fluids for up to 5 hours.

**EXAMPLES OF THE INVENTION**

25

Without thereby limiting the scope of the invention some examples will now be described to illustrate the invention. Preparations which do not as such form part of the claimed subject matter of this application, being preparations first disclosed in the applicant's own prior patents referred to above, are first restated.

30

**PREPARATION 1**

**Preparing an aqueous nitrous oxide solution**

35

A pressure vessel is charged to its operating volume with water at 20°C [ambient temperature]. The vessel is connected to a supply of nitrous oxide via a flow control valve and pressure regulator. The closed vessel is supplied with nitrous oxide at a pressure of 2 bar for a period of 48 hours, it having been determined that at the aforementioned temperature the water is saturated with nitrous oxide over such period of time under the

40



A resultant solution is bottled as stock solution for use in the formulations and applications set out below.

5

## **PREPARATION 2**

### **Preparation of nitrous oxide/Vitamin F aqueous emulsion**

- 30g Vitamin F ethyl ester as identified and described above was mixed with 10g Cremophor RH40 (which is the trade name used by BASF for a product which it describes as the reaction product of hydrogenated castor oil with ethylene oxide which product is also known by the INCI name as PEG-n-Hydrogenated Castor Oil), 2,2g methyl paraben, 0,08g butyl hydroxyanisole, 0,23g butyl hydroxytoluene with stirring at 80° C.
- 15 Into 942,5g of the stock nitrous oxide solution was dissolved 2,5g sodium propyl paraben and 2,5g Germall 115 [Imidurea] with stirring at room temperature.
- 20 The oily composition first described was emulsified into the aqueous solution with stirring to constitute a stock nitrous oxide/Vitamin F emulsion. It is herein referred to as "Lindil", "MZL" or "nanolipid-vesicle" formulation.

25

## **PREPARATION 3**

### **Preparation of a non-aqueous solution of nitrous oxide in carrier formulation.**

- 30 The Manufacturing Process for producing a non-aqueous formulation of an anti-infective agent according to the invention will now be described with reference to the manufacture of a first anti-TB medicament containing Pyrazinamide as active ingredient and a second anti-TB medicament containing the combination of Rifampicin, Isoniazid and Ethambutol as
- 35 active ingredients. These products are respectively designated as "Preparation P" and "Preparation RIE" herein.

**Preparation P** was made up according to the following protocol:

- 40 **Step 1:** Weigh off the Pyrazinamide 5,00Kg and reduce the particle size to less than 40µm.



**Step 3:** Gas the oil mixture with nitrous oxide for 3 hours at 2 bar in the stainless steel pressure vessel in the manner as described above.

5 **Step 4:** Transfer to mixing pot 1 and continue to mix.

**Step 5:** Weigh off and add the Methyl paraben 50,00g, Ascorbyl palmitate 10,00g and the Butylated hydroxytoluene 5,00g to mixing pot 1, while continuously mixing ensuring each solid is dissolved before adding the next.

**Step 6:** Remove from the heat and allow to cool down to approximately 40°C.

15 **Step 7:** Check the pH and add Potassium hydroxide while continuously mixing until the pH reads 7.

**Step 8:** Add the Rifampicin 1,467Kg, Isoniazid 733,00g and Ethambutol 2,20Kg, respectively, each stepwise allowing mixing after each addition.

**Step 9:** Gas with nitrous oxide at 20kPa for 30 minutes with mixing until the mixture has reached room temperature.

25 The Preparation P and Preparation RIE formulations were encapsulated in soft gel capsules in the manner well known in the pharmaceutical trade as oral capsules for use as described below.

### EXAMPLE 1

#### 30 ENHANCEMENT OF ANTI-BACTERIAL ACTION

This example pertains to the enhancement of current treatment modalities of infectious bacterial diseases.

35 The increased efficacy of antibiotics carried by nanolipid-vesicle in the treatment of bacterial infectious diseases was demonstrated by:

(a)

and (b) Bacterial culture studies (Bactec studies and confocal laser scanning microscopy CLSM);

40 (c) Infection studies involving live confocal laser scanning microscopy (CLSM) studies; and



- (d) Zone of Inhibition studies according to the USP XXIII zone inhibition method.

The following organisms considered to be representative and hence demonstrative albeit not exhaustive of the range of organisms to which the invention relates, were used in the above studies to confirm the invention:

*Mycobacteria Tuberculosis* (ref strain H37RV)

*Mycobacteria Tuberculosis* (MDR strains V79 & V25)

*Bacillus of Calmette and Guerin* (BCG)

*E Coli*

*S. Aureus*

*P Aeruginosa*

*B. Cereus*

*A. Niger*

*C. Albicans*

The anti-infective agents in the form of anti-bacterials used in these studies, and again considered to be representative and illustrative of the wide application of the invention, albeit not exhaustive, were Rifampicin, Ethambutol, Isoniazid, Pyrazinimide and Povidone-iodine, Cloxacillin, Erythromycin E, Ciprofloxacin, Co-trimoxazole (Sulfamethoxazole and Trimethoprim combination) and Itraconazole.

As will appear from the results discussed below the tests conducted on formulations involving the association of the active ingredient with the carrier prepared as set out in Preparation 2 above, showed a 10 to 40-fold enhancement of the efficacy of selected anti-infective agents compared to conventional formulations thereof.

#### **A. Bacterial culture studies:**

- (a) **The effect of the nanolipid vesicle encapsulation on the action of known anti-mycobacterials in BACTEC determinations.**

##### **(i) General Methodology of Collection and cultivation of Samples and Evaluation**

Clinical Isolates of *M. tuberculosis* banked at the Medical School at Tygerberg Hospital were cultured on L-J slant cultures and used for



BACTEC analysis. Drug sensitivity determinations in respect of the strains were done. *M.tuberculosis* strains were selected from a bank of 1800 clinical isolates genotyped according to their IS6110 insertion sequence profiles. The insertion sequence ranges from 1 to 23 copies per strain. These strains have been clustered into families according to their genetic patterns and represent recent transmission clusters because of their most frequent appearance in the community. These strains may also represent more virulent strains although virulence factors in M.Tb. have not yet been clarified.

The mycobacterial strains were carefully selected according to their genetic and epidemiological type. Multi drug resistant (MDR) strains were selected over a wide range from mildly resistant to highly resistant for Isoniazid, Rifampicin, Ethambutol and Pyrazinamide. Clinical and laboratory strains of *M.tuberculosis* were cultured in a medium enriched with ADC enrichment medium with continuous stirring to ensure homogenous bacterial distribution and uniform aeration as described by Middlebrook, G. (1977) in "*Automatable radiometric detection in growth of mycobacterium tuberculosis in selective media.*" **Ann. Rev. Respir. Dis.** 115:1066-1069. Under these conditions, cultures grow reproducibly (<1.0% difference). This technique was established in the Medical Biochemistry laboratory at Tygerberg Hospital.

At a culture density of approximately  $A_{600nm}=0.16$  (1x McFarland), (Siddiqui, S. H. (1995). **BACTEC 460 MTB system. Product and procedure manual.**) M.Tb. strain cultures were inoculated into BACTEC vials. Cultures in BACTEC were grown until a growth index (GI) of  $500(\pm 50)$  was reached. This culture was used as starter culture for BACTEC evaluation of carrier encapsulated antimycobacterial drugs. BACTEC growth of cultures was monitored over a period of 6-10 days and the  $\Delta GI$  value for every 24-hour doubling period determined. Every series of experiments were repeated at least 4 times to allow for accurate statistical analyses. Controls, with no drugs, were brought to the same concentrations. Sterility of mycobacterial cultures were monitored by Ziehl-Nielsen staining.

All experiments with infectious material should be carried out in a category 3 bio-safety laboratory. All experiments should be carried



out in such a way as to ensure maximum safety for all other laboratory co-workers.

**(ii) Evaluation in respect of Rifampicin**

Lindil, also referred to as the nanolipid vesicle formulation was prepared as described in Preparation 2 above and Rifampicin dissolved at a concentration of 80 micrograms per ml, was used in an initial evaluation of the effect of the preparation on M.tuberculosis cultures in BACTEC. This Lindil/Rif preparation was sterilized by filtration through 0.45 micron filters so as not to give background contamination by other bacteria.

M.tuberculosis Rifampicin resistant patient isolates were acquired from the South African Institute for Medical Research (SAIMR). Strains TV25 and TV79 were acquired from the strain bank at Tygerberg Hospital. Both were determined to be resistant to Rifampicin, Isoniazid and also streptomycin. The catalase activity of TV79 was found to be negative and that of TV25 to be 5mM.

Rifampicin was made up in 50% ethanol at a concentration of 10µg/ml. Eight µl were added to 1ml Lindil to give a concentration of 80µg/ml Lindil. Of this, 0.1 ml was added to a BACTEC vial to give a final concentration of 2µg/ml Rifampicin in Lindil. This is the cut-off value at which M.tuberculosis strains are evaluated for drug resistance or drug sensitivity for Rifampicin.

**Results:** It was found that Rifampicin in Lindil kills drug sensitive strains of M.tuberculosis to a much greater extent than Rifampicin alone at concentrations below 2µg/ml. Microscopy illustrated delivery of Rifampicin by Lindil into the interior of the bacillus, and these results show that the Rifampicin does not stay encapsulated in the bacillus, but is released from the nanolipid vesicle to the bacilli internal environment for biological activity. Lindil alone has no bactericidal effect at the concentration employed in this determination.

It was further found that the Rifampicin resistant strain used displayed increased Rifampicin sensitivity when Rifampicin is delivered to the bacilli via Lindil.



### Calculations:

Figures in the highlighted column (6) were used to calculate the effect of Ethambutol on mycobacterial growth in the absence of MZL. At this point the untreated TB control is GI=540. This is also the point where the TB growth becomes stationary (decline in growth). All GI values in this column were calculated relative to the control value of 415 to give % inhibition of growth. Column (9) shows the MZL treated control at approximately GI=415. All GI values in this column (Ethambutol in the presence of MZL) were calculated relative to the control value of 415 to give % inhibition of growth. The untreated control value was normalized to 415 to make results comparable. The results of the calculations are set out in Table 2.

**Table 2**

		Plus MZL	Minus MZL
		% Inhibition	% Inhibition
1.0 µg/ml	Ethambutol	86	92
0.5 µg/ml	Ethambutol	62	81
0.25 µg/ml	Ethambutol	51	51
0.125 µg/ml	Ethambutol	52	-12
0.0625 µg /ml	Ethambutol	49	-16
0.0325 µg /ml	Ethambutol	48	-21

### Results:

The results show that the MIC for Ethambutol in M.tuberculosis H37Rv strain is around 1.0 µg/ml. Results clearly show that from 0.125µg/ml Ethambutol, MZL presence still maintains a strong inhibitory effect on mycobacterial growth compared to MZL untreated bacteria whereas there was no growth inhibition. In fact, a slight stimulation of growth (negative values) is observed. This is usually observed with very low antibiotic manipulations. At the higher Ethambutol concentrations (0.25-1.0µg/ml) there does not appear to be much difference in growth inhibition between MZL treated and untreated. The very high concentrations appear to have a better effect in the untreated M.Tb. This effect could be a dose response because of the very high presence of Ethambutol at the high concentrations. In the MZL treated experiments it appears as though MZL captures Ethambutol in its structure making less



Ethambutol freely available for diffusion over the mycobacterial membrane. However as the concentrations become lower it appears that MZL gives a steady delivery of Ethambutol to the M.Tb. with the result that inhibition is steadily maintained (approx 50% inhibition over the range of 0.03125µg/ml-0.125µg/ml).

From these results it appears that MZL maintains steady state delivery of Ethambutol to the M.Tb. over the spectrum of concentrations used and this effect is most prominent in the low concentration range of MZL that is the concentration range significant for therapeutic efficacy.

**(b) The effect of nanolipid-vesicle encapsulation of the antibiotic Pyrazinamide on the resistance of BCG (Bacillus of Calmette and Guerin) to Pyrazinamide:**

The encapsulation of antibiotics Isoniazid, Ethambutol and Rifampicin into the nanolipid vesicles formulation of Preparation 2 described above resulted in a product suitable for use in the inhibition of Mycobacterium Tuberculosis in bacterial isolates from patients infected with both drug-sensitive and multidrug resistant strains. The results were obtained with the Bactec system, with no human cell involvement.

The significance of the following result stems from the fact that the BCG vaccine is extensively used for vaccination against infection by *Mycobacterium Tuberculosis* (*M.Tb.*). BCG vaccine is classified as a non-pathogenic mycobacterial strain and is therefore a widely used investigative model of infection by (*M.Tb.*). All BCG strains are resistant to Pyrazinamide (see Morbidity and Mortality Weekly Report; 1996, vol 45, No RR-4). The effect of encapsulation of this antibiotic by nanolipid vesicles according to the Invention and its delivery in that form to BCG was investigated.

In this investigation which was performed by confocal laser scanning microscopy (CLSM), use was made of a live/dead fluorescent stain known as *BacLight*. It stains live bacteria green and dead bacteria red. General viability of the BCG's was determined by the green/red ratio of the bacteria. The effect of equal amounts and concentrations of free and nanolipid-vesicle encapsulated Pyrazinamide on BCG viability was investigated.



**Bacterial viability:** The general viability of the BCG 's before any addition of antibiotics was between 85 – 95%. The BCG-viability after a two-hour incubation of the applicable dosage of free Pyrazinamide was 68 –72%.

**Bacterial growth characteristics:** BCG generally grows in clumps. Incubation with free Pyrazinamide resulted in the appearance of single live bacteria with a few granuloma-type clumps, which gradually secrete single live bacteria. The single live bacteria were mobile. Encapsulation of Pyrazinamide in nanolipid-vesicles led to a 65-75% decrease in BCG viability within a two-hour incubation. No moving BCG was observed.

Accordingly, BCG prelabelled with live/dead *BacLight* bacterial stain and then treated with nanolipid-vesicle encapsulated Pyrazinamide was observed by confocal laser scanning microscopy. It was found that, after an hour, most of the bacteria were labelled red, and were therefore dead. No granuloma-type clumps or single bacteria were observed. Such clumps and single bacteria, all coloured green, were seen in the control in which the same quantity of Pyrazinamide in water alone was brought into contact with BCG also prelabelled with live/dead bacterial stain.

The study thus yielded the most surprising result that bacterial resistance to Pyrazinamide may be overcome by encapsulation of the antibiotic into the nanolipid vesicles composition of Preparation 2.

### **(c) Infection studies (Live confocal laser scanning microscopy studies)**

In this study the aim was to determine whether encapsulation of an antibiotic by nanolipid vesicles gives rise to a product by which one could overcome resistance of intracellular bacteria, using infection of human macrophages by BCG in culture as a cell model.

The THP1 macrophage cell line (ATCC) was used for the infection study. RPMI 1640 with L glutamine cell culture medium, Foetal Bovine Serum and phosphate buffered solution (Gibco BRL), were used for cell growth according to general cell culture methods.



THP1 macrophage cells were cultured and infected with pre-treated labelled BCG bacteria. Treatment consisted of equal concentrations **namely 0.075 µg/ml** of free and nanolipid-vesicle encapsulated Pyrazinamide. CLSM was used to determine infection by and survival of the bacteria.

The viability of BCG's after infection in macrophages reflects that BCG's inside macrophages treated with nanolipid-vesicle associated Pyrazinamide is effectively killed by the antibiotic Pyrazinamide, even though the bacteria are generally recognised to be resistant to the antibiotic used.

**(d) Zone of Inhibition Studies:**

**(i) Enhancement of Povidone iodide against two bacterial organisms as evidenced by zone of inhibition studies.**

Inhibition of bacterial growth of two types of bacteria by the active ingredient known as Povidone iodine in formulated form with the nanolipid vesicles of Preparation 2, and so used at a concentration of 6.30g Povidone iodine equivalent to 0.75g available Iodine in 100g of product, was compared with the effect of the same amount and concentration of the free active ingredient. The bacteria were S. Aureus and P.Aeruginosa. The control used was saline.

The results obtained in the study are graphically represented in the graph which is Figure 2 hereto. It is clear that inhibition of bacterial growth in both types of bacteria is dramatically increased when the active is associated with the nanolipid vesicles.

**(ii) Enhancement of five anti-infective agents against five different bacterial organisms**

Five commercially available antibacterial compositions containing the active ingredients set out in Table 3 below were compared in zone inhibition studies with saline as control with compositions of the same active ingredients made up in a carrier according to the invention. These are designated "MZL" formulations in the case of aqueous made according to preparation Z above and "MZLA" formulations in the case of non-aqueous formulations prepared according to Preparation 3 above. This



convention is also followed in other examples below as opposed to the commercial formulations (COM) of particular active agents. The compared formulations were diluted where necessary to achieve the same concentrations.

5

It is evident from the results set out below that the organisms were more sensitive to the active agents when encountered in the carrier formulation according to the invention.

10



- 5 a) The delivery and transport function of the nanolipid-vesicles increase the therapeutic efficacy of AZT ten fold at a dilution of 1:512 base formulation, thereby creating the possibility of decreasing the AZT dosage 10 fold, as is shown by the relative effect of 1nM free AZT versus 0.1 nM nanolipid-vesicle formulated AZT. The results clearly show that the addition of 0.1nM free AZT inhibited viral growth and replication by 44% by day 7 and 8, when compared to the control (no AZT added). However, the addition of 10 0.1nM nanolipid vesicle-associated AZT inhibited viral growth by between 70 - 80% on day 8. This is comparable to the inhibition observed by 1nM free AZT (i.e. 10 times the concentration). Furthermore, addition of 0.1nM nanolipid vesicle-associated AZT showed a continued decrease in viral load over 8 days, whereas the addition of 15 even 10x that amount of free AZT resulted in a decrease in viral load up to day 6, after which the viral growth increased slightly.
- 20 b) The graphs in Figure 2 show that the association of AZT with nanolipid vesicles changes the pharmacokinetics and possibly the intra-cellular biodistribution of AZT.
- 25 c) The effective delivery of the basic nanolipid vesicle formulation has been established for CD4 T-cells and macrophages to be a dilution of between 1:512 and 1:1024 of the concentrated unfiltered formulation. Higher content of nanolipid vesicles appears to favour viral growth in the cells. At a dilution of base-formulation (1:256), viral inhibition is optimal at a higher concentration of AZT (0.5 - 30 1nM).

35 Note that no correction has been made in the above evaluation for the contribution of the cells itself to the Absorbance/cut-off ratio. It was considered to be negligible (>0.4).

### Conclusions:

- 40 a) The administration medium of Preparation 2 at the correct dilution may be used to decrease the effective therapeutic dosage of AZT by as much as 10 fold. It would considerably decrease the cytotoxicity of the AZT treatment. At such low dosages, it may



be more attractive to treat expecting mothers for HIV infection, without any long-term side effects on the foetus.

- b) Optimisation of nanolipid vesicle concentration for AZT-delivery is essential, as unloaded nanolipid vesicles can favour the multiplication of HIV viruses by supplying components for viral membranes synthesis and energy for viral metabolism, as the metabolism of nanolipid vesicle essential fatty acids (EFAs) may increase the energy status of the cell, and therefore also the energy available to the HIV virus for its replication. The nanolipid vesicle concentration must therefore be sufficient to serve only its transport function, without supplying either membrane components or energy for viral multiplication.

The changed pharmacokinetics and intracellular biodistribution of AZT transported by nanolipid vesicles are probably the result of the following two mechanisms:

- a) the change in environment with regards to charge and hydrophobicity when nanolipid vesicles move from the extracellular to the intracellular environment, and  
b) the normal cellular pathways of the EFAs, which include its metabolism in the mitochondria. The release of AZT is therefore most probably in the region of the mitochondria.

### Example 3

#### **Yeasts and fungi: The enhancement of agents used in the treatment of Infectious Diseases caused by Yeasts and Fungi.**

The use of this invention for the enhancement of agents used in the treatment of yeasts and fungi (moulds) was investigated and established by the following studies described in greater detail below, namely:

Comparative culture studies  
Infection studies (Live CLSM imaging)  
Zone inhibition.

#### **(a) Comparative culture studies:**

Fungi of the mycosis type was grown in culture medium (RPMI 1640 with L glutamine cell culture medium) at 37°C at 90% humidity, 5% CO<sub>2</sub> for a week. Equal aliquots of grown fungi were exposed to nanolipid vesicles loaded with a commercially available antifungal agent containing 2% Miconazole nitrate. Comparison was made with free Miconazole nitrate



i.e. the commercially available form of that active ingredient. In both instances the exposure was at a final concentration of 0.4% over similar time periods (30 minutes to 18 days), using a single initial dosage.

5 **Results:**

The nanolipid-vesicle delivery system can be used for the efficient delivery of antifungal agents to fungi.

- 10 Miconazole nitrate association with nanolipid vesicles, but not free Miconazole nitrate caused a fast and unexpectedly dramatic decrease of the fungi as illustrated in Table 4.

15 **TABLE 4**  
**VIABILITY OF FUNGI AGAINST TIME ELAPSED AFTER SINGLE**  
**EXPOSURE TO MICONAZOLE NITRATE**

<b>Time</b>	<b>Nanolipid-vesicle encapsulated Miconazole</b>	<b>Free Miconazole</b>
30 min	5%	80%
4 hours	0%	70%
11 days	0%	30%
18 days	1%	15%

20 **(b) Infection studies:**

- 25 Two equal aliquots of melanoma cells (UCT Mel 1 cell line) were incubated for 4 hours with fungi and 0.2% of either free Miconazole nitrate or Miconazole nitrate formulated with the administration medium of Preparation 2 in order to test the effect of the formulation in terms of the invention on the efficacy of fungal treatment of human cells.

- 30 The viability of both human melanoma and human macrophages was found to decline dramatically in the presence of free Miconazole nitrate but not when the Miconazole is encapsulated in nanolipid vesicles. The result is graphically presented in Figure 4 hereto.

- 35 **Figure 4** shows the viability of both the human melanoma and fungi 4 hours after the addition of the therapeutic agents in a petri dish.



Using a macrophage cell line, the same result was obtained.

Melanoma cells were healthy after 4 hours incubation with nanolipid-vesicle encapsulated Miconazole nitrate and no fungi was present. In the presence of free Miconazole nitrate, cells were no longer attached to the petri dish and fungi were still present in large numbers.

**(c) Zone of inhibition studies:**

Zone of inhibition studies on yeasts and moulds namely C. Albicans, T. Mentagrophytes and E. Floccosum were also carried out. Inhibition of yeast and mould growth by the active ingredient Miconazole nitrate in association with nanolipid vesicles was observed. The control used was saline.

The result of this study is reflected in Figure 5 hereto

**Conclusion:**

It is quite clear from the results presented in Figure 5 that the active Miconazole nitrate in association with the nanolipid vesicles inhibits the growth of both yeasts and moulds and does so to a greatly enhanced extent.

**Example 4**

**Parasitology: The treatment of Infectious Diseases caused by parasites:**

**Summary:**

The effect of free and non-aqueous nanolipid formulated chloroquin made according to the process described in Preparation 3 against a resistant Falciparum strain (the reference strain W2 for drug resistant malaria) was preliminarily determined in the conventional manner. The strain is known to have a 50% Inhibition concentration value ( $IC_{50}$ ) of between 200-300 nmolar Chloroquine. The determined  $IC_{50}$  value for nanolipid formulated Chloroquine was about one tenth of the value for free chloroquine, namely 25-30 nmolar. This most surprising result holds substantial promise for further research as its utilisation in practice means that malaria would be capable of being treated with greatly reduced cytotoxicity and resulting lower incidence of side effects. In addition drug cost will also be lower.



## Approach and general Method

5 The specific parasite investigated was the reference drug resistant strain W2 of the species *Plasmodium Falciparum*. *Plasmodium Falciparum* is the most commonly occurring as well as the most virulent malaria parasite currently known in man.

10 The system used in this investigation aims to mimic the live situation as closely as possible. For that reason, the parasites were infected into fresh primary erythrocytes isolated from O+ or A+ blood donors.

15 Furthermore, human serum prepared from the same donors was used as an adjuvant instead of foetal calf serum. Parasite growth was maintained by the addition of freshly prepared erythrocytes from the same donors.

20 The growth of the parasites was determined by visualization of the parasite DNA on thin smears of the infected cultures. Since mature erythrocytes contain no nucleus, and therefore no DNA, the only DNA present was of parasitic origin. Only intracellular parasites were included in determining the percentage parasitaemia, as extracellular parasites are no longer viable.

### Protocol:

25 The protocol was typical for work of this nature and included the following steps as will be readily apparent to those skilled in the art.

#### 30 A. Culturing of malaria parasites:

1. Preparation of fresh human erythrocytes
2. Preparation of human serum from the same donor.
3. Quality control of human serum.
- 35 4. Infection of erythrocyte cultures with parasites. Initial infection load was 0.5% parasitaemia.
5. Maintenance of parasite blood cultures
6. The parasite percentage in the blood cultures was determined after 36 or 48 hours, depending on the level of infection of the freshly added erythrocytes.

40

#### B Basic toxicology:



Determination of possible toxic effect of nanolipid formulations on erythrocytes and parasite growth.

The following nanolipid formulation concentrations were investigated:

5 0. 1:1500, 1:1000; 1:750; 1:500; 1:250; 1:100; undiluted.

C Loading of nanolipid formulation with chloroquine:

10 A stock solution of 10mM chloroquine solution in a 1:250 dilution of nanolipid formulation was made by vortexing and sonication. All concurrent dilutions were from this stock.

D Drug delivery by MZL nanolipid formulations:

15

1. Penetrance of nanolipid formulations in red blood cells was determined by microscopic visualization, as were the penetrance of chloroquine-carrying nanolipid formulations.

20

2. The drug concentration series used centred around the known IC50 concentration of chloroquine in the W2 strain.

25

3. Typically 48-well plates or 96-well plates were used. 200ul or 100ul total culture volumes were used respectively, of which 90% of the volume was infected erythrocyte culture. 10% volume was used for the treatment, be it chloroquine in Nanolipid formulation, chloroquine in water, or for the controls 1:250 pure Nanolipid formulation, pure culturing media or water only.

4. All series were in duplicate.

30 E Visualization of Intracellular parasites:

Parasitic DNA was visualised by Giemsa staining of thin smears.

Ethidium bromide or acridine orange may be used for fluorescent staining.

35 F % Parasitaemia:

The % infection after applicable incubation periods was determined as follows:



Total parasite count per 10 microscopic fields

-----x 100%

Total cell count per 10 microscopic fields

5

#### G Quality assurance of counting:

10 All counts of the first series were undertaken by two scientists. The results correlated very well. The second series was spot-checked by a second scientist, especially around crucial concentrations. Once again no significant deviations were found between the two sets of results.

#### Results:

15 The counts of the cultures are reflected in the table 5 below:

**TABLE 5**

	CLQL				CLQ			
Chloroquin e concentrati on	Cells/ field	Total cells	Para- sites	% Parasit + MZL	Cells/ field	Total cells	Para- sites	% Parasit
0 nM	95	950	17	1.8	73	730	16	2.19
1nM	87	870	18	2.06	127	1270	34	2.67
5nM	127	1270	29	2.88	60	600	14	2.33
10nM	130	1300	37	2.84	135	1350	40	2.96
25nM	120	1200	23	1.91	130	1300	37	2.84
50nM	90	900	13	1.41	111	1110	30	2.7
75nM	54	540	5	0.9	129	1290	43	3.33
100nM	125	1250	14	1.1	64	640	18	2.81
200nM	106	1060	4	0.3	108	1080	31	2.87
300nM	88	880	13	1.41	105	1050	19	1.8
500nM	63	630	7	1.1	76	760	0.15	1.5
1000nM	87	870	12	1.3	71	710	10	1.4



W2= Chloroquine resistant strain internationally recognized and used.

CLQL = Chloroquine in 1:250 dilution MZL nanolipid carrier; concentrations of chloroquine as indicated.

CLQ= Chloroquine in medium at the specified concentrations.

Resistant strains become sensitive only at very high Chloroquine concentrations.

Association of chloroquine with nanolipid formulation results in a similar susceptibility as sensitive strains.

Statistical analysis of the results was by Chi-square analysis between the two sets of data. A combination of the 3 repeats of the two sets of data gives a Chi-square value of 7.6. According to the probability tables, the difference between pure chloroquine and MZL-associated chloroquine is highly significant, with only a 0.0001 probability that the difference observed between the two treatments is due to chance.

#### 10 **Conclusions:**

1. The association of chloroquine with MZL nanolipid formulation significantly decreases the  $IC_{50}$  of chloroquine (by 6x to 10x).
2. Primary human cells show high tolerance for the MZL nanolipid formulation, with cytotoxicity only observed at high extremely high concentrations.
3. MZL formulations may be used in the prophylaxis of drug resistant malaria.



**Example 5****Comparative release properties as determined by Membrane Diffusion of Anti-infective agents formulated in accordance with the present invention and commercially available formulations of the same anti-infective agents.****1. OBJECTIVE**

The scope of this study was to establish whether the Test Anti-infectives Acyclovir and Miconazole Nitrate are released from the dosage form of the invention at a satisfactorily rate and extent in comparison to the commercially available Comparators.

The applicability of the test method for release out of the dosage forms was confirmed by *Handbook of Dissolution Testing: Dissolution Testing of Transdermal Delivery Systems*, page 61. The small receptor volume to be used, in this case 12 ml, is confirmed in the same reference on page 63, which refers to 5 – 25 ml.

**2. METHOD**

The in vitro release from the dosage forms was determined by a Hanson Model 57-6M, Manual Start-Up, Diffusion Cell Test System bought from Hanson Research with the following main parts:

CELL DRIVE CONTROL  
6-CELL DRIVE WITH CELLS  
VERTICAL CELLS

**3. PARTS NEEDED**

1. Diffusion cell assembly, including donor top and receptor chamber (set of 6). The donor top includes a drug dosage wafer (Teflon washer), an acrylic top plate, and a clamp to connect top to bottom.
2. Pig skin used within 24 hours from being slaughtered kept in Ringer Solution between 2°C - 8°C.
3. Davies Gold Series Dermatome, Simplex GS 102.
4. Application squeegee and tweezers.
5. Drug dosage form.
6. Absorbent paper towels and tissues.

**4. TECHNIQUE**

1. Obtain skin from pig heads (jawbone skin). Use Dermatome according to the Operation standard operating procedure for the Dermatome, setting it to size the skin to a thickness of



0.33mm. The diameter of the skin should be in excess of the drug dosage wafer.

2. Prepare receptor chamber of diffusion cells with slight overflow of medium (pH 5 buffer with glacial acetic acid for the Test Product Acyclovir and 6.8 phosphate buffer for the test product Miconazole) with temperature controlled at 32°C.

3. Prepare each piece of skin with the relevant products one at a time as follows:

3.1. Lift skin with tweezers, place on tissue and blot excess of solution, invert and blot.

3.2. Place skin in centered position on drug dosage wafer.

3.3. Place relevant products on top of skin in dosage wafer cavity – 0.5 ml by means of a Gilman pipette – weighed and averaged to obtain dosage applied.

3.4. Use squeegee to carefully smooth product over membrane, filling entire cavity.

3.5. Wipe excess dosage water with squeegee.

3.6. Lift loaded dosage wafer with skin and place on top of receptor cell with skin side towards cell medium. Exclude bubbles during process. Place on top of donor cell assembly, pressing down with finger, squeezing out bubbles between top plate and dosage form. Apply clamp to lock down top donor and bottom receptor halves of diffusion cell.

## 5. OPERATION OF APPARATUS

The apparatus must be set to 150 rpm. Samples of 150µl are withdrawn with a micropipette at 2', 5', 8' and 10' and 15 minutes. The samples after being withdrawn are analysed for Acyclovir and Miconazole Nitrate respectively by means of HPLC according to the parameters set out in Table 6 below.



**Table 6**

	Acyclovir	Miconazole Nitrate
Injection volume	20 $\mu$ l	20 $\mu$ l
Column	Zorbax SB C18 250mm x 4.6mm	Zorbax SB C18 250mm x 4.6mm
Mobile Phase	0.02M GAA in H <sub>2</sub> O pH 3.5	70% Methanol 30% H <sub>2</sub> O +1% GAA
Detector	HPLC at 254nm	HPLC at 224 nm
Temperature	Ambient (22°C)	Ambient (22°C)
Flow Rate	1.5 ml per min	1.5 ml per min
Retention Time	20.8 – 21.9 min	9.4 –9.9 min
Solvent	MP adjusted to pH 5	Methanol
Cells used	3 (1 for Comparator)	6
Time at which total release determined (Min)	15	60

## 5 6. RESULTS

The release experiment was performed in the number of cells indicated above for each product and the mean release is reported for each analysis point. The results are tabulated and graphically presented. The results as a percentage of the active released per label claim per cell at the different time intervals is also tabulated.

In Table 7 below is shown a summary of the release rate and percentage release per label claim for the products determined according to calculations, reporting the mean values of the utilised number of cells of each product after the effluxion of the time indicated above.

**Table 7**

**Table indicating release rates and percentage release per label claim for product tested.**

Active Agent	% Active /product	Release Rate ( $\mu$ g/cm <sup>2</sup> /h)	% Release per label claim
Acyclovir MZL	0.5	69.1533	0.1214
Acyclovir COM	0.5	54.0942	0.0952
Miconazole Nitrate MZL	2	389.9238	6.8155
Miconazole Nitrate	2	111.2222	1.9466



## 7. CALCULATIONS

5 The Release Rate was calculated as follows:

### 7.1. $\mu\text{g}$ Active Released at time (min.)

$$10 \quad = \frac{A_{\text{sam}} \times \text{Mass Std} \times \text{Vol Receptor} \times \text{Mass of Active Applied for Z cells} \times C}{A_{\text{std}} \times \text{Vol Std} \times \text{Label Claim} \times \text{Mass of Product Applied for 1 cell} \times Z \times 100}$$

#### WHERE:

	<b>A sam</b>	=	Area of peak sample solution
	<b>A std</b>	=	Area of peak of standard solution
15	<b>Mass std</b>	=	Mass of standard taken to prepare the standard solution expressed in $\mu\text{g}$
	<b>Vol Std</b>	=	Volume to which the standard solution is made up, expressed in ml
20	<b>Label Claim</b>	=	Amount of active present per 100g of product
	<b>Mass of Product Applied for 1 cell</b>	=	Specific amount of product applied for a specific cell
25	<b>Mass of Active Applied for Z cells</b>	=	Amount of active applied in total for all Z cells utilised per one study
	<b>C</b>	=	potency of the standard, expressed as a percentage

### 30 7.2. Accumulative Dose ( $\mu\text{g}$ ) released /square cm at time (min)

$$= \frac{\mu\text{g Active Released}}{(\text{Surface Area of Exposed Skin})}$$

$$35 \quad = \frac{\mu\text{g Active Released}}{1.767 \text{ cm}^2}$$

### 40 7.3. Release Rate

$$= \frac{\text{Accumulative Dose } (\mu\text{g}) \text{ released / square cm}}{\text{Time (hours)}}$$



#### 7.4. Percentage of Active Released at time (min.)

$$= \frac{\mu\text{g Active Released} \times 100}{\mu\text{g Active Applied}}$$

#### 8. CONCLUSION

From the foregoing test it was concluded that the formulation according to the invention

(a) releases Acyclovir 1.28 faster than the Comparator Acyclovir formulation at 15 minutes, and continues to release higher quantities throughout the duration of the test;

(b) releases Miconazole Nitrate 3.51 times faster than the commercial Comparator at 60 minutes.

#### Example 6

#### **DEMONSTRATION OF THE EQUIVALENT OR IMPROVED BIOAVAILABILITY OF ANTI-TB DRUGS IN THE FORMULATION ACCORDING TO THE INVENTION COMPARED TO A COMMERCIALLY AVAILABLE PRODUCT**

##### **1. BACKGROUND:**

Anti-tuberculosis treatment presents with two major problems- the development of drug resistance and compliance. The nanolipid based delivery system provides a system for single or combination tuberculosis drug treatment with a significantly increased therapeutic index, using currently prescribed anti-tuberculosis drugs, with a resultant decrease in the development of drug resistance. The delivery system contains the same therapeutic moieties but differs in chemical form, and dosage of those moieties and can therefore be regarded as a pharmaceutical alternative. Furthermore, the higher therapeutic index of the drug facilitates lower dosage, which limits the side effects, which may in its turn be expected to improve compliance. Using this delivery system, delivery of the drugs may also be expanded to tissues usually not easily reachable by current therapeutic regimes.

The formulated delivery system contains components that have been recognized as pharmaceutically safe. The public health authority of South Africa in concert with many other health authorities, advise the same actives as used in this investigation as initial treatment regime for all tuberculosis patients. This protocol describes the delivery of the



prescribed anti-TB drugs in 4 single daily doses by way of the delivery system at a reduced dosage level to 1 healthy volunteer.

In an open crossover design, pharmacokinetic parameters of the four drugs delivered by the test formulations in reduced doses were compared to those achieved when the same drugs were administered in the reference formulations of established quality and in the standard treatment doses. The volunteer was monitored daily during the study. The protocol below describes the dosage level, the specific drug, the time period of the study, the parameters investigated and the combinations of drugs used.

## 2. STUDY OBJECTIVES

### *Primary Objectives*

The first primary objective of this investigation was to determine the bioavailability of generally used anti tuberculosis treatment agents, i.e. Rifampicin (R), Isoniazid (H), Ethambutol (E) and Pyrazinamide (Z), each packaged into the MZL drug delivery system in the form of the capsules produced in the manner as described in Preparation 3 above.

Secondly, it was to determine changes in patient global assessment, i.e. significant change from baseline of the following pharmacokinetic parameters:

- a) peak plasma concentration (C<sub>max</sub>),
- b) the time needed to reach this concentration (T<sub>max</sub>),
- c) exposure (the area under the plasma curve (AUC 0-9 hours), and
- d) coverage.

The pharmacokinetic results were compared with those of reference formulations. The packaged drugs were administered at an equal or a decreased dosage of that in the commercially available combination antituberculosis drugs.

### **2.2 Secondary objectives**

The secondary objectives of the investigation were

firstly, to determine whether bioequivalence exists for drugs packaged into the delivery system by comparison to reference agents;



secondly, to determine whether there are changes in the status of side effects caused by the actives;

5   thirdly, to determine the relative safety levels of the comparative products;

fourthly, to determine possible partitioning of the MZL nanolipid delivered drugs to cells and possible cytotoxicity as a result; and

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finally, to note the possible advantages to the volunteer's well-being (i.e. malaise, bone ache, nausea etc) when using the delivery system of the invention for the administration of anti-tuberculosis drugs.

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### 3. STUDY DESIGN

20   The treatment was based on the ***Standard Treatment Guidelines and Essential Drugs List (1998)***. The study design was an open crossover bioavailability design of tuberculosis drugs [Rifampicin (R), Isoniazid (H); Ethambutol(E) and Pyrazinamide(Z)] delivered by a formulated drug delivery system. Bioavailability is understood to be the rate and extent to which the active substance or therapeutic moiety is absorbed and

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delivered from a pharmaceutical form

a) into the general circulation and

b) becomes available at the site of action.

30   As in other bioavailability studies, the kinetics of the therapeutic moiety in the general circulation was monitored in this study.

The study was conducted over two periods of 4 days each, interrupted by a two week wash out period. During the last day (day 4) of each period, blood samples will be taken at the times specified below to determine

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several pharmacokinetic parameters. Blood samples (10ml each) were taken at the following intervals after administration of the drugs: 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 9 hours.

#### 3.1 Rifampicin:

40

The volunteer received the currently commercially available prescribed Rifampicin, namely Rifampin, treatment for 4 consecutive days, followed



by a wash out period of 2 weeks. Rifampin contains Rifampicin as active ingredient. The volunteer then received pure Rifampicin packaged into the nanolipid delivery system of the invention as described above at two thirds of the prescribed dosage, again for 4 consecutive days. This nanolipid formulation of Rifampicin is herein also referred to as Rifemzaloid. The volunteer took the medication in the morning before a meal with 200ml of tea, as food has been shown to influence absorption. Meals were standardized and supplied a couple of hours after first administration of the medication.

### 3.2 Combination Drugs:

The volunteer started with two third dosage of all four drugs packaged into the nanolipid delivery system of the invention, followed by the same scenario with the commercially available treatment regime, namely Rifafour, after a two week wash out period. The volunteer took the medication in the morning before a meal with 200ml of tea, as food has been shown to influence absorption. Meals were standardized and supplied a couple of hours after first administration of the medication.

### 3.3 General Protocol Requirements:

- a) The subject volunteered for participation in the study. The volunteer was a Caucasian middle-aged female and was clinically healthy i.e. blood chemistry, full blood count and liver function tests of subjects fell within the normal ranges. The volunteer granted written informed consent before participating in the study.
- b) All drugs were orally administered in Soft Gel capsule form at applicable doses. The volunteer did not take any other chronic medication during the study.
- c) The study was single blind for laboratory procedures. Plasma level assays of the actives were performed in the conventional manner.
- d) Blood and liver function assays were undertaken in the conventional manner.
- e) The safety of the treatments was assessed according to the ICH Clinical Trial Guidelines. No serious adverse events (AE) occurred during the study.



#### 4 TREATMENT REGIME:

##### 4.1 Pharmaceutics

5 The nanolipid delivery system formulated as described above was used as a base for the active drugs used when comparing the pharmaceutical efficacy of drugs delivered by a delivery system with the generally prescribed drugs containing identical actives.

##### 10 4.2 Dosing:

###### **Rifampicin:**

15 Commercially available Rifampin tablets (600mg) were taken daily for four consecutive days, followed by sample collection on day 4.

20 Nanolipid formulated Rifampicin was taken in the same manner but at two thirds of the above dosage, i.e. 400mg Rifampicin encapsulated in the delivery system. Dosing was again followed by a sample collection in order to determine the comparative pharmacodynamic profile of the active.

###### **Combination treatment:**

25 The generally prescribed drug regime, consisting of 5 combination tablets Rifafour RHZE (120 /60 / 300/200 mg) were taken daily for 4 consecutive days, after which blood samples were collected for plasma concentration analysis.

30 In the nanolipid combination formulation, 5 capsules containing a two third dosage of each of the actives i.e. RHZE 100/40/200/132mg were taken and analysed in the same manner.

##### 35 4.3 Study Supplies

40 The drugs used in the study were packaged into the nanolipid delivery system, manufactured according to Preparation 3 above and labelled in accordance with Good Laboratory and Manufacturing Practice (GLP and GMP) Guidelines for the labelling of study medication as set out in Table 8 below.



**Table 8****4.4 Sample Collection and Preparation**

Blood (10ml) was collected at specified times for HPLC determination of the plasma concentrations of Rifampicin. Blood was also collected for liver function determinations and full blood cell counts.

Samples were collected in heparinized tubes and placed immediately on ice. Plasma was extracted by centrifugation within 15 minutes of collection and stored at a minimum of minus 80°C.

<b>Prescribed treatment: RHZE combination tablet</b>			
<b>Dosage:</b>	<b>RHZE mg/tablet</b>	<b>RHZE mg/day</b>	<b>RHZE mg/week</b>
Less than 50 kg	120/60/300/200	480/240/1200/800	2400/1200/6000/4
more than 50 kg	120/60/300/200	600/300/1500/1000	3000/1500/7500/5
<b>Drugs administered by drug delivery system</b>			
<b>Drug delivered/treatment</b>	<b>Drug mg/capsule</b>	<b>Drug mg/day</b>	<b>Drug mg/week</b>
Rifampicin, R	100mg	400mg	2000mg
Isoniazid, H	100mg	200mg	1000mg
Pyrazinamide, Z	250mg	1000mg	5000mg
Ethambutol, E	132mg	660mg	3300mg
<b>Prescribed treatment: RHZE combination tablet</b>			
<b>Dosage:</b>	<b>RHZE mg/tablet</b>	<b>RHZE mg/day</b>	<b>RHZE mg/week</b>
Less than 50 kg	120/60/300/200	480/240/1200/800	2400/1200/6000/4
more than 50 kg	120/60/300/200	600/300/1500/1000	3000/1500/7500/5
<b>Drugs administered by drug delivery system</b>			
<b>Drug delivered/treatment</b>	<b>Drug mg/capsule</b>	<b>Drug mg/day</b>	<b>Drug mg/week</b>
Rifampicin, R	100mg	400mg	2000mg
Isoniazid, H	100mg	200mg	1000mg
Pyrazinamide, Z	250mg	1000mg	5000mg
Ethambutol, E	132mg	660mg	3300mg

Blood samples were collected and handled in accordance with Good Clinical Procedures (GCP) Guidelines.

**4.5 Plasma concentration determination**

The concentrations of Rifampicin(RIF), Isoniazid(INH) and Pyrazinamide(PZA) and their active metabolites were determined by



high performance liquid chromatography after their simultaneous extraction from plasma. The materials used were INH, RIF, PZA and pyrazinoic acid; HPLC - grade acetonitrile, methanol and trifluoroacetic acid (TFA) and C18 Bondelut extraction columns, 200mg, 3 ml 40 microns.

The plasma concentrations of RIF were determined using a mobile phase of 80% acetonitrile in 0.1% trifluoroacetic acid. A reversed phase C8 analytical column (Spherisorb, 250 X 4.6 mm ID, 5µm) linked to a C8 precolumn, with flow rate at 2.0 ml per minute and detection at 270 nm was used.

For the determination of INH and PZA, the mobile phase was 3% acetonitrile in 0.06% TFA. A reversed phase C8 analytical column (Spherisorb, 150 x 4.6 mm ID, 5µm) linked to a C8 pre-column with flow rate at 1.5 ml per minute and detection at 254 nm was used.

#### *Stock standards*

A stock standard solution of Rifampicin (0.5mg/ml), PZA(0.5 mg/ml) and INH(0.5 mg/ml) and pyrazinoic acid were prepared (0.5 mg/ml) is prepared in Methanol.

Relative retention times were established by spiking and comparing peak area ratio of RIF.

#### **INH and PZA.**

All stock solutions are kept at a minimum of 4°C and protected from light.

#### ***Specificity***

Analyses of blank samples of the appropriate biological matrix were tested for endogenous interferences in the reference standard region for RIF, INH and PZA.

Calibration graphs (peak areas vs concentration) were constructed for RIF and INH in the range 0.1-20µg/ml and for PZA in the range 0.1-60µg/ml. INH, RIF and PZA and pyrazinoic acid analysis were done in triplicate.

Intra- and inter-assay coefficients of variation were determined.



Five replicate samples of four concentrations were run through the procedure with exactly controlled volumes, as described for the extraction of the samples. To verify recovery/quality control, precision and accuracy, the peak areas obtained for the extracted samples were be compared to those of fresh standards of the analytes in mobile phase with respect to the volumes handled during extraction.

C18 Bondelut extraction cartridges were washed sequentially with 2 x 2 ml of methanol, 2 x 2 ml of water and 2ml of 0.05 M potassium phosphate, pH 4.5 (phosphate buffer) prior to application of the sample to the columns.

A 0.5 ml quantity of plasma were thawed and drawn slowly onto the column and allowed to stand for 5 minutes, after which time unbound material were discarded. The columns were washed with 1 ml of phosphate buffer to be discarded, and the drugs eluted with 0.5 ml of acetonitrile, followed by 0.5 ml of methanol with these elutes being pooled.

60 µl of the pooled eluates were injected immediately onto the HPLC column to assay for RIF.

***INH, PZA and pyrazinoic acid:***

0.5ml of the combined eluates were dried by vacuum centrifugation and taken up in 0.5 ml of 3% acetonitrile in 0.06% TFA.

60µl of this were injected onto the autosampler HPLC to assay for INH and PZA, which were detected together on the same column.

**Acceptance criteria:**

A validated analytical method meets the following criteria:

**Precision and accuracy:** The between batch CVs for low, medium and high concentrations should be <15%, and 20% for the LOQ QC.

**Sensitivity:** The lowest standard should be accepted as the LOQ if the %CV is <20%

**Specificity:** The responses of interfering peaks at the retention time of the analyte should be less than 20% of the response of an LOQ standard.



**Stability:** Stock solution stability should meet the criteria specified in the SOP.

## 5. RESULTS

### 5.1 Comparative bioavailability of Rifampicin

The first part of the study concerned only Rifampicin and the nanolipid-formulated Rifamzaloid. The plasma levels determined for the indicated times are reflected in Table 9.

TABLE 9 Plasma levels of Rifampicin		
Time(min)	MZLA Rifamzaloid ( $\mu\text{g}$ Rif /ml plasma)	Rifampicin ( $\mu\text{g}$ /ml plasma)
0	0	0
30	10.31	0
60	12.93	7.46
90	11.23	10.23
120	11.22	9.3
150	10.16	8.43
210	8.82	9.03
240	10.03	7.39
370	9.27	6.32
300	7.22	4.84
330	6	4.1
360	5.77	3.45

### Increased Cmax

The maximum plasma concentration (Cmax) of Rifampicin was determined to be 12.93 $\mu\text{g}$ /ml and was reached 60 minutes (Tmax) after oral administration of the active in the nanolipid delivery system. The Cmax obtained for the Rifampin (10.23 $\mu\text{g}$ /ml) was reached 90 minutes after administration. The delivery of Rifampicin to the plasma was therefore increased by at least 21% at Tmax by the nanolipid carrier. Furthermore, only two thirds of the normal



dosage was taken in the MZL formula. Therefore, the increased delivery of Rifampicin to plasma by the Nanolipid delivery system at Tmax was 181% that of its comparator at equal dosages.

## 5 **Decreased Tmax**

10 The minimum effective concentration of Rifampicin in plasma is 7µg/ml. It is clear from the results that Rifampicin reaches its effective concentration much quicker when delivered by the Nanolipid delivery system. This is especially important in the case of unstable drugs such as Rifampicin, as increased gastric exposure may lead to increased loss of activity.

## 15 **Increased Coverage**

20 Coverage can be regarded as the time period during which the effective concentration is maintained. Figure 6 illustrates that the coverage afforded by using the nanolipid delivery system is increased by 180% (270 minutes vs 150 minutes). It is therefore possible to the increase the time intervals between sequential dosages.

25 The above parameters reflect the comparative bioavailability dynamics of the Nanolipid delivery system. The total average increase in bioavailability by Nanolipid delivery system was 227%, while using only two thirds of the dosage of the comparator.

30 Differences in the above pharmacodynamic and pharmacokinetic parameters were statistically significant (see Table 10), with a p-value of 0.0157. The statistical method for analysis used was Analysis of Variance with a single factor variant.

**TABLE 10**  
**SUMMARY OF STATISTICAL ANALYSIS**

<i>Groups</i>	<i>Count</i>	<i>Sum</i>	<i>Average</i>	<i>Variance</i>
Column 1	11	103.16	9.378182	4.944216
Column 2	11	70.45	6.404545	9.408267

### ANOVA

<i>Source of Variation</i>	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>P-value</i>	<i>F crit</i>
Between Groups	48.63382273	1	48.63382	6.77706	0.017005894	4.351250027
Within Groups	143.5248364	20	7.176242			



Figure 6 hereto records the observed bioavailability of Rifampicin in the MZL formulated Rifamzaloid vs its comparator Rifampin. The comparative daily Rifampicin dosages were 400mg/ day in the case of Rifamzaloid and 600mg/day in the case of Rifampin.

## 5.2 Bioavailability of Combination Drugs

Similar results were obtained with Isoniazid and Pyrazinamide. Figure 7 hereto illustrates the enhancement in bioavailability of INH, using the nanolipid delivery system, and Figure 8 that of Pyrazinamide (PZA).

**Figure 7** shows the enhanced bioavailability of Isoniazid when encapsulated in the MZL delivery system, even though the daily dosage of the INH in the MZL formula was only two thirds of that of the comparator, Rifafour.

**Figure 8** illustrates the enhanced bioavailability of Pyrazinamide in the MZL formulation. Again the daily dosage of the PZA in the MZL formula was only two thirds of the PZA in Rifafour, the comparator.

## 5.3 Side effects:

No significant side effects were found with the MZL formulated liver function analysis. None of the liver enzymes showed levels higher than the normal range. The S-unconjugated bilirubin, which did show levels elevated above the normal range was nearly back to normal 8 hours after drug administration, and was normal on the following day.

## 5.4 Volunteer's assessment:

The only adverse reaction to either of the MZL formulas (Rifampicin or Combination) was nausea, whereas the comparator Rifafour led to serious headache, jitters and nausea.

## 5.5 Partitioning of nanolipid formulated Rifampicin:

Between 5-10% of the Rifampicin encapsulated in the nanolipid partitioned to blood cells rather than to plasma. This partitioning should increase the effective dosage



delivered to the cells, but the partitioning is not so high as to be cytotoxic.

5 The study was repeated for Rifampicin and Pyrazinamide with similar results.

Many modifications of the invention may be devised without departing from the spirit and general scope of the invention.



**CLAIMS**

1. A method of enhancing the action of an anti-infective agent  
5 characterised in that the agent is selected from the group comprising antimicrobial agents, the anthelmintic agents and the anti-ectoparasitic agents, but excluding coal tar solution and H1-antagonist antihistamines, comprising the step of formulating the agent with an administration medium which comprises a solution of  
10 nitrous oxide gas in a pharmaceutically acceptable carrier solvent for the gas and which medium includes at least one fatty acid or ester or other suitable derivative thereof selected from the group consisting of oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, arachidonic acid, eicosapentaenoic acid [C20: 5 $\omega$ 3],  
15 decosahexaenoic acid [C22: 6 $\omega$ 3], ricinoleic acid and the derivatives thereof selected from the group consisting of the C1 to C6 alkyl esters thereof, the glycerol-polyethylene glycol esters thereof and the reaction product of hydrogenated natural oils composed largely of ricinoleic acid based oils, such as castor oil, with ethylene oxide.  
20
2. A pharmaceutical preparation comprising an anti-infective characterised in that the agent is selected from the group comprising antimicrobial agents, the anthelmintic agents and the anti-ectoparasitic agents, but excluding coal tar solution and H1-  
25 antagonist antihistamines, which agent is formulated with an administration medium which comprises a solution of nitrous oxide gas in a pharmaceutically acceptable carrier solvent for the gas and which medium includes at least one fatty acid or ester or other suitable derivative thereof selected from the group consisting of  
30 oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, arachidonic acid, eicosapentaenoic acid [C20: 5 $\omega$ 3], decosahexaenoic acid [C22: 6 $\omega$ 3], ricinoleic acid and the derivatives thereof selected from the group consisting of the C1 to C6 alkyl esters thereof, the glycerol-polyethylene glycol esters thereof and  
35 the reaction product of hydrogenated natural oils composed largely of ricinoleic acid based oils, such as castor oil, with ethylene oxide.
3. The method of claim 1 or the preparation of claim 2 which contains  
40 a mixture of esters of the essential fatty acids set out in those claims and is preferably constituted by the complex known as Vitamin F Ethyl Ester having a typical fatty acid distribution as follows:



< C<sub>16</sub>: 0  
 C<sub>16.0</sub> : 8,3 %  
 C<sub>18.0</sub> : 3,5 %  
 C<sub>18.1</sub> : 21,7 %  
 C<sub>18.2</sub> : 34,8 %  
 C<sub>18.4</sub> : 28,0 %  
 > C<sub>18</sub>: 1,6 %  
 unknown: 2,1 %

- 10 4. The method or the preparation of claim 3 wherein the administration medium further includes eicosapentaenoic acid [C20: 5 $\omega$ 3] and/or decosahexaenoic acid [C22: 6 $\omega$ 3] as additional long chain fatty acids and/or the reaction product of hydrogenated castor oil and ethylene oxide known as PEG-n-Hydrogenated Castor Oil.
- 15 5. The method of claim 1 or the preparation of claim 2 wherein the carrier is water (preferably deionised water) or any of the pharmaceutically acceptable alcohols, ethers, polymers such as a polyethylene glycol or the like or an oil which is preferably an organic oil which organic oil is further preferably an essential oil based on long chain fatty acids having between 14 and 22 carbon atoms in the fatty acid and is preferably of natural origin and most preferably a plant oil rich in gamma linolenic acid [GLA].
- 25 6. The method of claim 1 or the preparation of claim 2 wherein the anti-infective agent is formulated in a liquid or encapsulated liquid presentation for oral administration or in a nasal or bronchial or pulmonary spray or in the form of an injectable formulation and wherein the formulation incorporate, as part of the administration medium, water or acceptable other liquid into which the nitrous oxide is dissolved, preferably to saturation, and wherein the fatty acid or ester thereof is either dissolved or suspended or emulsified along with the anti-infective agent.
- 35 7. The method of claim 1 or the preparation of claim 2 wherein the anti-infective agent is formulated as a topical, buccal or vaginal cream or ointment, or as a suppository, and wherein the formulation used in making up such cream, ointment or suppository incorporates, along with the anti-infective agent to be enhanced, a quantity of water or other liquid containing, and preferably saturated with, nitrous oxide, the long chain fatty acid or ester thereof and the anti-infective agent formulated therewith, and,

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optionally further incorporates such additional excipients and carriers as are conventionally used in the pharmaceutical trade in making up such dosage forms.

- 5 8. The method of claim 1 or the preparation of claim 2 wherein the carrier solvent for the nitrous oxide gas is essentially non-aqueous and composed of at least one fatty acid or ester thereof selected from the group consisting of oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, arachidonic acid, eicosapentaenoic acid  
10 [C20: 5 $\omega$ 3], decosahexaenoic acid [C22: 6 $\omega$ 3], ricinoleic acid and derivatives thereof selected from the group consisting of the C1 to C6 alkyl esters thereof, the glycerol-polyethylene glycol esters thereof and the reaction product of hydrogenated natural oils composed largely of ricinoleic acid based oils with ethylene oxide,  
15 required to be part of the formulation.
9. The method of claim 1 or the preparation of claim 2 wherein the anti-microbial agent is selected from the groups consisting of :  
20 the anti-bacterial agents (including both antibiotics and substances other than antibiotics such as the sulfonamides, the erythromycins and other macrolides, the aminoglycosides, the tetracyclines, the chloramphenicols and the quinolones);  
the anti-fungal agents;  
the anti-viral agents (including anti-retroviral agents);  
25 the anti-protozoal agents;  
the tuberculostatics;  
the anti-leprotics;  
the germicides;  
and  
30 the spirochaeticides.
10. The method of claim 1 or the preparation of claim 2 wherein the anti-infective agent is selected from the group comprising: the anthelmintics, the anti-ectoparasitcides, the anti-bacterial agents  
35 (including both antibiotics and antibacterial substances other than antibiotics); the antifungal agents; the anti-viral agents; the anti-protozoal agents; the tuberculostatics; the anti-leprotics; the germicides; and the spirochaeticides.
- 40 11. The method or the preparation of claim 9 wherein the anti-infective agent comprise at least one tuberculostatic selected from the group consisting of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol.



12. The method or preparation of claim 11 wherein the anti-TB formulation is prepared to be adapted for pulmonary administration.

5 13. The method or the preparation of claim 9 wherein the anti-infective agent comprise at least one of the ingredients selected from the group consisting of Acrosoxacin, Acyclovir, Amantadine, Amicacin, Amifloxacin, Amikacin, Aminosalicyclic Acid, Amoxicillin, Amphotericin B, Ampicillin, Apalcillin, Azidamphenicol, Azithromycin, Azlocillin, Aztreonam, Bacampicillin, Bacitracin, Bacitracin Zinc, Benzoic Acid and Salicyclic Acid, Benzyl penicillin (Penicillin G), Butoconazole, Capreomycin, Carbenicillin, Carfecillin, Carindacillin, Cefaclor, Cefadroxil, Cefalexin, Cefamycins, Cefdinir, Cefepime, Cefetamet Pivoxil, Cefixime, Cefmenoxime, Cefodizime, Cefonicid, Cefoperazone, Ceforanide, Cefotaxime, Cefotetan, Cefotiam, Cefoxitin, Cefpiramide, Cefprozil, Cefsulodin, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefuroxim, Cefuroxime Axetil, Cephaloridine, Cephmandole, Cephazolin/Cephadrine, Cephadrine, Cetatriazine, Chloramphenicol, Chloramphenicol, Chlortetracycline, Ciclopirox, Ciclopirox Olamine, Cinoxacin, Cipofloxacin, Ciprofloxacin, Clarithromycin, Clavulanic Acid, Clindamycin, Clofazimine; Clotrimazole, Cloxacillin, Colistin (Colisten Sulfate), Co-Trimoxazole (Trimethoprim + Sulphamethoxazole), Cycloserine, Dapsone, Demeclocycline, Dicloxacillin, Didanosine, Doxycycline,

25 Econazole, Enoxacin, Enrofloxacin, Erythromycin, Ethambutol, Ethionamide; Famciclovir, Fleroxacin, Flucloxacillin, Fluconazole, Flucytosine, Fluxonazole, Foscarnet, Ganciclovir, Gentamicin, Gentamicin Sulfate, Glycylcyclines, Griseofulvin, Haloprogin, Hetacillin, Idoxuridine, Imidazoles, Imipenem, Interferons Alfa, Intrathecal, Iodide, Isoniazid, Itraconazole, Kanamycin, Ketoconazole, Lamivudine, Latamoxef (Oxacephalosporin), Levofloxacin, Lomefloxacin, Loracarbef, Mafenide Acetate, Menazopyridine, Meropenem, Metaampicillin, Methacycline, Methenamin, Methicillin, Mezlocillin, Miconazole, Miningal, Minocycline; Nadifloxacin, Nafcillin, Naftifine, Nalidixic Acid (Oxolinic Acid), Natamycin, Neomycin, Netilmicin, Nitrofurantoin, Norfloxacin, Nystatin, Ofloxacin, Oxacillin, Oxiconazole, Oxytetracycline, Pefloxacin, Penciclovir, Phenoxymethyl-Penicillin (Penicillin V), Phthalylsulphathiazole, Pipemidic Acid, Piperacillin, Piromidic Acid, Pivampicillin, Pivcephalexin, Pivmecillinam, Polymyxin B (Polymyxin B Sulfate), Potassium Iodide, Propionic Acid And Caprylic Acid,



Pyrazinamide, Ramoplanin (Glycopeptide), Riampin, Ribavirin,  
Rifabutin, Rifampin, Rimantadine, Roxithromycin, Rp 59500,  
Rufloxacin, Silver Sulphadiazine, Sorivudine, Sparfloxacin,  
Spectinomycin, Stavudine, Streptomycin, Succinylsulphathiazole,  
5 Sulbactam, Sulconazole, Sulfacetamide Sodium, Sulfadoxine,  
Sulfametopyrazine, Sulfisoxazole Diolamine, Sulphacetamide,  
Sulphadiazine, Sulphadimethoxine, Sulphadimidine, Sulphafurazole,  
Sulphaguanidine, Sulphamethoxazole, Sulphamethoxydiazine,  
Sulphamethoxypyridazine, Sulphapyridine, Sulphasalazine,  
10 Talampicillin, Tazobactam, Teicoplanin (Glycopeptide), Temocillin,  
Terbinafine, Terconazole, Terconazole, Tetracycline, Tetracycline  
Hydrochloride, Thiamphenicol, Ticarcillin, Tioconazole, Tobramycin,  
Tobramycin Sulfate, Tolnaftate, Tosufloxacin, Trifluridine,  
Undecylenate, Undecylenic Acid, Valacyclovir, Vancomycin,  
15 Vidarabine, Vidarabine, Zalcitabine, Zidovudine.

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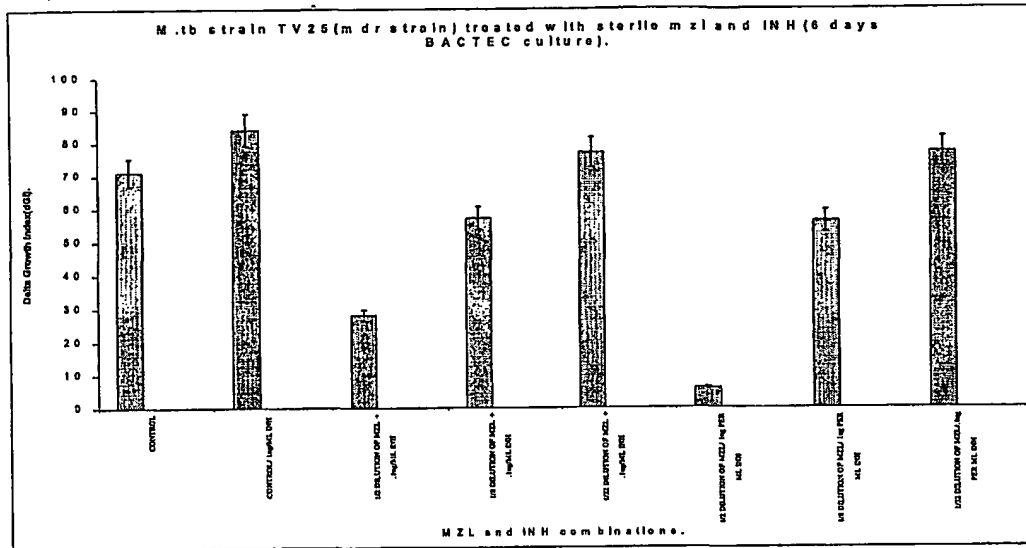
1.  
/  
4

FIGURE 1

## Zone inhibition by different therapies

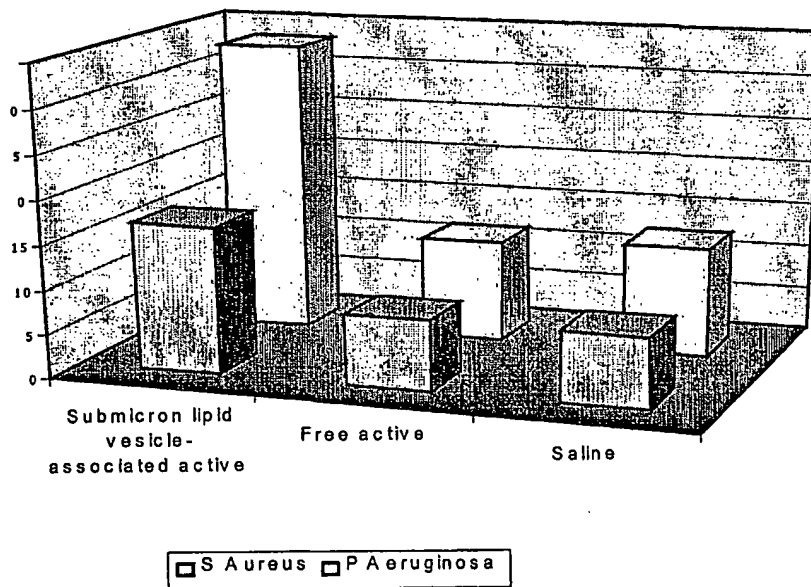


Figure 2



2  
/  
4Absorbance/cut-off  
ratios

CD 4 T-cell and viral growth

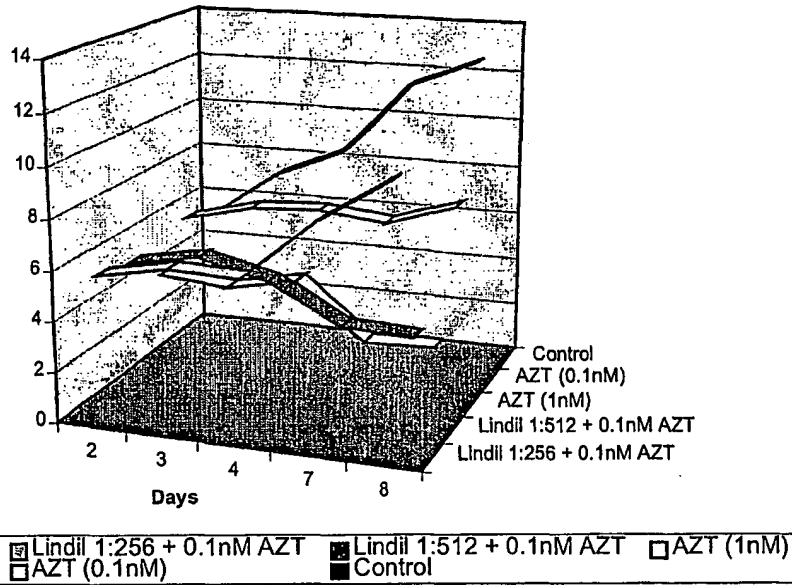


FIGURE 3

Viability of Me11 cells

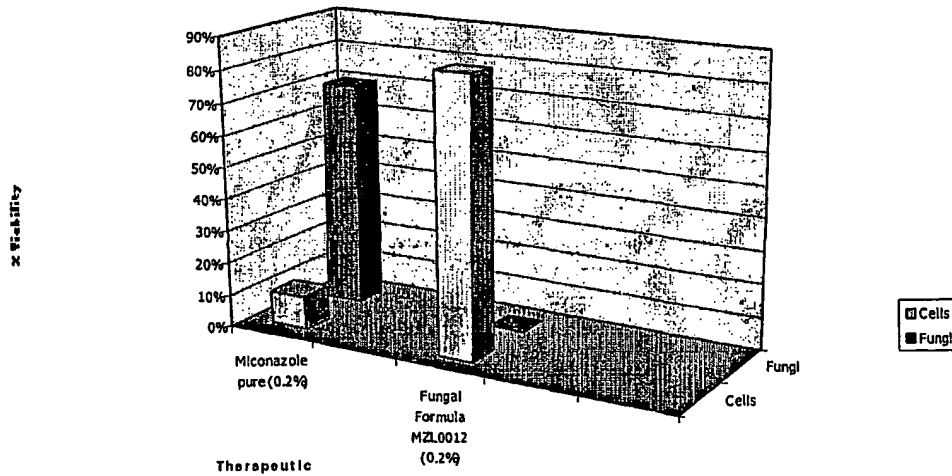


FIGURE 4



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Zone Inhibition measured

Zone Inhibition of yeasts and molds

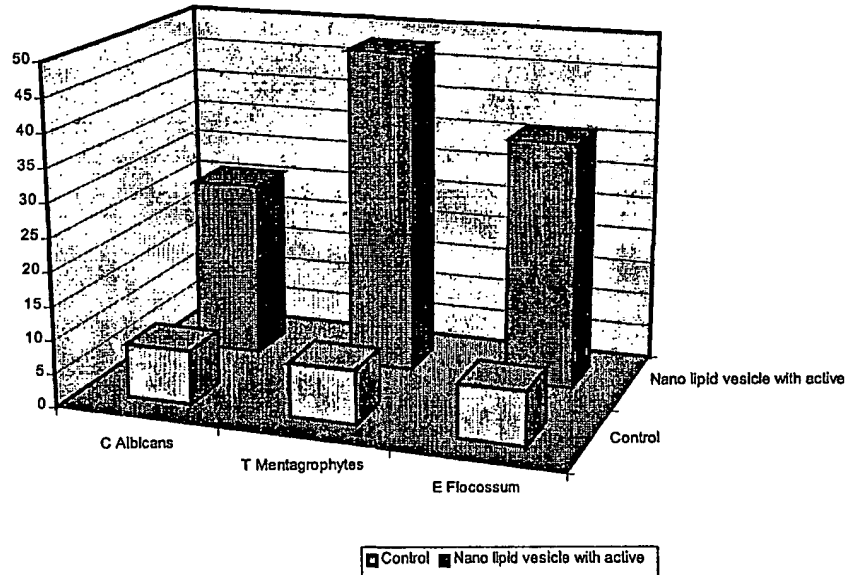


Figure 5

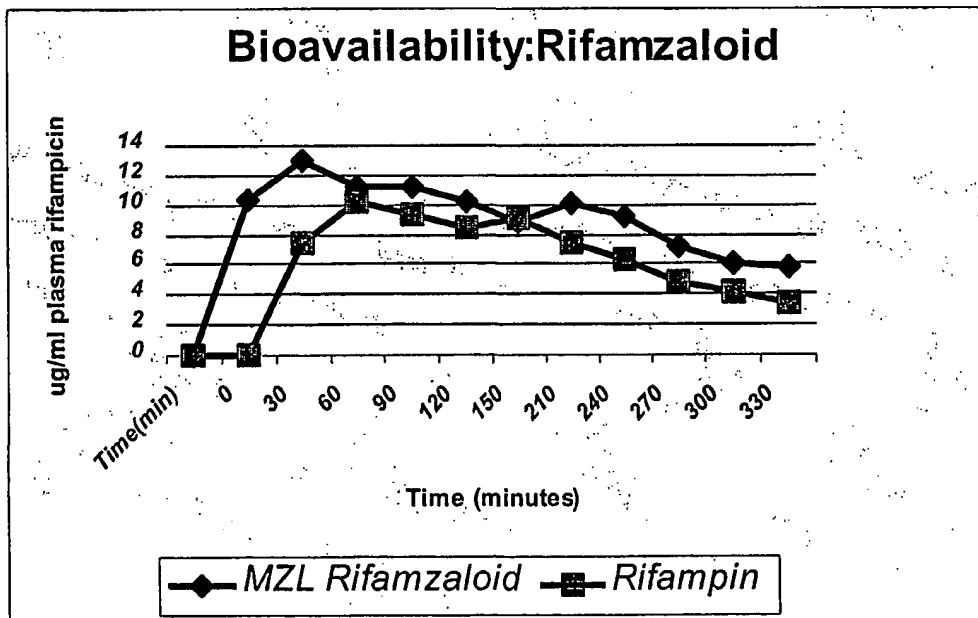
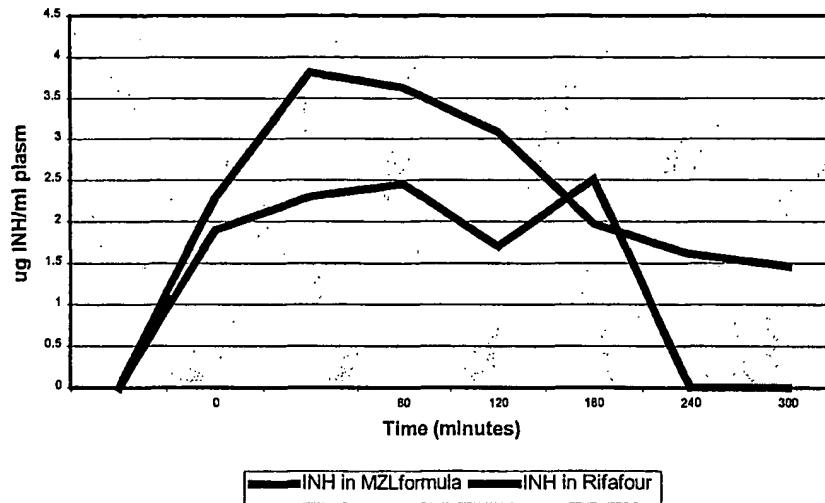
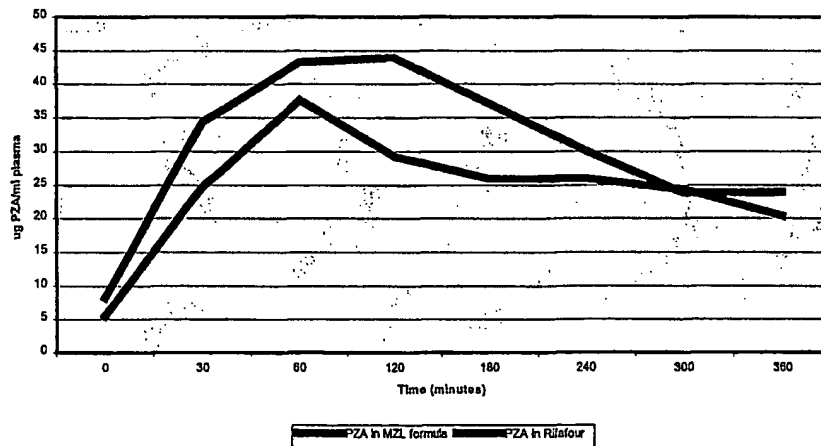


Figure 6

**Bioavailability of Rifampicin in the MZL formulated Rifamzaloid vs its comparator Rifampin**



4  
/ 4**BIOAVAILABILITY OF IZONIAZID****Figure 7****Bioavailability of IZONIAZID****BIOAVAILABILITY OF PYRAZINAMIDE****Figure 8****Bioavailability of Pyrazinamide**



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